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P R O C E E D I N G S

(8:40 a.m.)

DR. TAMMINGA: I would like to call this meeting to order and welcome everyone to the 39th meeting of the psychopharmacologic drugs advisory committee.

My name is Carol Tamminga. I am from the Maryland Psychiatric Research Center at the University of Maryland. I am the chairperson of the committee.

Next, I would like those seated around the table to introduce themselves.

(Introductions were made.)

DR. TAMMINGA: Mr. Bernstein, who is the executive director of this committee, would like to say some introductory things.

Agenda Item: Opening Comments.

MR. BERNSTEIN: Thank you, Dr. Tamminga. I would like to welcome each of the committee members to this, the 39th meeting of the psychopharmacologic drugs advisory committee. My name is Mike Bernstein and I am the executive secretary of this committee, which functions within the division of neuropharmacological drug products. Please bear with me while I make a few

administrative announcements.

On the table by the entry are hand outs of the entry, agenda list, and roster of committee membership. We ask that all speakers speak directly into a microphone.

Individuals from the audience, following recognition by the chair, should come forward to a microphone. Unless one speaks directly into the mike, comments cannot be heard by all transcriptionists, nor by those of us sitting in the rear of the room.

If anyone in the audience desires to make any comments in the open public hearing, we ask that you wait until you have been recognized by the chair before coming forth to a mike.

Please identify yourself and your affiliation before beginning your statement. Statements made in the open public hearing must relate to the issue being considered at this meeting and be of general interest to the committee members.

Smoking is not permitted in this building and, obviously, in this conference room. For those of you who desire a quick lunch, the cafeteria is directly behind us on the opposite side of the building.

A lunch break will be determined according to the schedule that we have at hand, and we will make an announcement later on.

As this is an open meeting, a reminder that the proceedings may be tape recorded, but that the recording is considered to be unofficial until it has been approved by the Commissioner of Food and Drugs.

The following announcement addresses the issue of conflict of interest and is made a part of the record to preclude even the appearance of such at this portion of the meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, the agency has taken the following action to preclude even the appearance of a conflict of interest.

The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interests.

However, the agency has determined that the need for the services of those participants who are affiliated with a university and/or hospital which could potentially be affected by the

committee's deliberations, outweighs the potential for a conflict of interest created by the financial interests involved.

Therefore, institutional waivers have been granted to all committee participants who are affiliated with a university and/or hospital.

In addition, full waivers have been granted to the following participants for their interests related to the particular matters coming before the committee today or the competing products: Drs. Abby Fyer, Carol Tamminga, Javier Escobar, Bob Hamer, Larry Ereshefsky, Dennis Charney and Ellen Frank.

A copy of these waiver statements may be obtained from the agency's Freedom of Information Office, Room 12-A-15 of the Parklawn Building.

Further, we would like to disclose for the record that, because of past involvements in studies of risperdal, Dr. Ereshefsky and Dr. Nina Schooler are excluded from participating in the discussions and voting related to risperdal.

In addition, Dr. Dennis Charney would like to disclose that his employer, the West Haven Veterans Administration Medical Centers, is currently involved in a study of risperdal and of a

competing product to risperdal.

Since Dr. Charney's interests are as an employee of the federal government, it has been determined that this is not a financial interest under 208, and he may participate fully in today's discussions.

In the event that the discussions involve any other products or firms not already on the agenda, for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask, in the interests of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

And finally, NDA 20-152, serzone, and NDA 20-272, risperdal, will be the only issues discussed by the committee at this meeting. Thank you for your attention and this concludes my comments, Dr. Tamminga.

DR. TAMMINGA: The open public hearing is now in progress.

Agenda Item: Open Public Hearing.

DR. TAMMINGA: No one has contacted Mr. Bernstein ahead of time to request an opportunity to address the committee. However, if anyone from the audience has any comments or statements to make about our business today, would they please come forward to a microphone, identify themselves, and proceed.

(No audible or visible response.)

DR. TAMMINGA: It seems like no one has any comments to make about the business of the day, so that the public hearing is closed.

The topic for today's advisory committee meeting, as Mr. Bernstein has already stated, is NDA 20-152, serzone, followed by an issue with NDA 20-272, risperidone. Dr. Tom Laughren, who is the group leader in the department of neuropharmacological drug products, will have the opening remarks.

Agenda Item: Open Session. SERZONE (Nefazodone HCL): Safety and Effectiveness in Use as an Antidepressant.

DR. LAUGHREN: I would like to welcome you to this 39th meeting of the psychopharm advisory committee. We have two items on the agenda today,

first nefazodone, and then later on this afternoon we are going to revisit risperidone, the drug that we talked about back in April.

First, nefazodone. Nefazodone is a new compound that has been proposed for use as an antidepressant. It has several pharmacological effects that are of interest. It is a 5 HT2 antagonist. It also inhibits the uptake of both serotonin and, at least in vitro, norepinephrine, and it has a weak alpha-1 blocking effect.

This drug is extensively metabolized and there are two metabolites that may have some importance in terms of their activity and the amounts present in plasma. The first one is hydroxynefazodone, and the second is tryazolodione.

I want to emphasize that our reviews on nefazodone are not entirely complete at this time. But we felt that we were far enough along in the review process to merit bringing this drug to the committee for your thoughts on its safety and effectiveness.

First, I would like to make a few comments about efficacy. Joy Mele, the biometrics reviewer, is going to present the efficacy data. She will be presenting these findings in great

detail. However, as a way of introducing what I think is a very complex data set, I thought it might be worthwhile for me to try to give a brief overview.

This may seem somewhat redundant, but I think this data set is complex enough that it might bear some repetition.

The regulatory question that we are focusing on is whether or not there is substantial evidence of efficacy from adequate and well-controlled trials to support the anti-depressant claim.

Our efficacy review has focused on eight short-term placebo-controlled studies. Two of these studies, when analyzed as a whole, I think, provide some evidence of effectiveness. Those are studies 004B and 005.

Now, 004B is a titration study involving two doses of nefazodone, one up to 600, one up to 300, and placebo.

The second study is 005, also a titration study, involving a nefazodone up to 600, imipramine up to 300, and placebo.

Now, even though those studies make it overall, there are some inconsistencies. For

example, in study 004B, it doesn't make it on the HAM-D Depressed Mood item. In 005, although the analysis overall is positive, it is clear, when you look at the centers from that study, that most of the positive outcome is coming from one of the two centers, the Family Practice Center, whereas the psychiatric center tends not to make it.

Of the other six studies, two, I think, provide some support. Those are studies 003 and 006. 003 is also a titration study, in this case involving two different dose ranges for nefazodone, one up to 500, one up to 250, and imipramine up to 250 and then placebo.

That study is generally positive on the high nefazodone dose, at least on the last observation carry forward analysis, but it doesn't make it on the observed cases analysis.

The other study, 006, is similar to 005. It involves three arms, one nefazodone arm up to 600, imipramine up to 300 and then placebo.

Now, the analysis for that study is not positive overall. However, there are two centers for that study. And if you analyze those centers separately, one is generally quite positive. The other is a failed center in which there is a very

high rate of drop out, and neither active drug beats placebo.

So, that takes care of four of the eight studies. Of the other four studies, three of them, I think, probably failed because of dose. The nefazodone dose was generally lower, and that may be a reasonable explanation for why those studies failed.

The fourth study, 004A, which is similar in design to 004B, in other words, two nefazodone doses and placebo, it is unclear why that study is negative.

My overall impression, again, is that there is evidence of antidepressant efficacy among these eight studies. However, I want to emphasize that the results here are mixed and there are some inconsistencies.

And this is a situation in which we are particularly eager to get your advice and your counsel.

I want to make one more comment about efficacy data before moving on to safety. The one other issue that I want to talk about is one that we have talked about at recent advisory committee meetings, and that is the question of, to what extent the sponsor has provided evidence or long-

term efficacy.

Depression, of course, is often a chronic illness requiring long-term treatment. And ideally, we would have some data to address the question of how long to continue a patient on therapy after response, and whether or not the drug has any relapse prevention effect.

Now, in fact, the sponsor has provided some data in this NDA in patients who were continued from the double blind short term trials for some period of time.

A meta analysis of those data are suggestive of long term effects. However, we believe there are some problems in drawing conclusions about data that are obtained in that manner, and that may be a topic that is worth some committee discussion.

The design that we generally prefer to address this question is the relapse prevention design, in which patients who respond on an open basis are then re-randomized to either continuation on drug with placebo for a long period of time.

Now I want to turn briefly to safety. Earl Hearst, the clinical reviewer for nefazodone, will present the safety data. Nefazodone was

recently approved in the UK but it is not yet marketed there or anywhere else. And our safety review is focused entirely on the premarketing studies that the sponsor has provided. And that involves roughly 2,700 patients exposed to nefazodone.

Our impression, based on our review, is that the adverse events that are associated with nefazodone can be easily handled through labeling. There is one issue that I think is of some interest, that may merit some discussion, and that is a very substantial pharmacokinetic interaction between nefazodone and triazolam.

Now, I want to make one final comment on nefazodone. As you notice, you have been provided with a copy of the sponsor's draft labeling in the package. This has been provided more as a summary than as a topic for discussion.

I want to emphasize that this is the sponsor's proposed labeling. It is not the labeling that would accompany any approval package if this drug were to be approved. We did not review this yet.

Our focus today is on the general questions of safety and effectiveness of nefazodone,

and not on the details of labeling.

Nevertheless, we would welcome any comments you might have on particularly important issues that pertain to labeling, but this is not a setting in which we can feasibly draft labeling for this product.

Now, the other topic that we are going to deal with, probably later this afternoon, is risperidone. Risperidone, of course, is a drug which was the subject of an April 29th meeting of this committee.

And at that time, the vote was unanimous in favor of both its safety and its effectiveness.

Now, subsequent to that meeting, we became aware of some findings from rodent carcinogenicity bioassays, which were somewhat unusual. And we thought it would be important to share those findings with you.

Since rescheduling risperidone for today's meeting, those data have been to the center's internal carcinogenicity assessment committee. And their recommendation has been to mention the findings and label them along with the usual statement about the fact that the relevance of those findings for humans is unknown.

And our plan at present is to implement that recommendation. Nevertheless, we thought it would be important to share this with you and, of course, you can discuss these findings. We have not planned to ask for any particular vote on this issue.

Glenna Fitzgerald, the supervisory pharmacologist for the division, will be making a brief presentation on pertinent data from those studies, and I believe the sponsor is also planning to make a brief presentation.

At this point, I would like to introduce Joy Mele from the division of biometrics, who is going to present the effectiveness data for nefazodone.

Agenda Item: FDA Presentation - Efficacy Review.

MS. MELE: Dr. Laughren has given you a good overall introduction to the efficacy data and now I will give you some of the details.

This is a brief outline of my presentation this morning. Even though my outline is brief, my presentation is not. So, if you have any questions, please interrupt me during the talk.

First, I will present a few definitions

to clarify the terminology I will be using throughout my presentation. Then I will present some general information about the efficacy trials.

Next, I will present the efficacy data for low dose nefazodone. Six of the eight placebo-controlled trials we will be talking about today had a low dose treatment arm. Even though the low doses used is less than the recommended dose for efficacy, I think it is useful to look at this data to understand the development of nefazodone, and also to see the relationship between the high and low dose.

The last part of my presentation will focus on the five studies in which high dose nefazodone was compared to placebo. This is the part I ask you to give your closest attention to, since the high dose data is critical for establishing the efficacy of nefazodone for the treatment of depression.

Primarily, two doses of nefazodone were studied. I will refer to these two doses as low and high dose nefazodone. Low dose is defined as peak doses less than or equal to 300 milligrams per day, while high dose is defined as peak doses greater than 300, but less than or equal to 600 milligrams

per day. For six of the eight studies, the dosing was BID.

I have included study center and site here, because during the review process, I found the sponsor and I were applying different meanings to these terms.

I consider sites as part of a single center, and centers as part of a multicenter study or trial.

Usually, sites consist of small numbers of patients and are geographically close to each other.

Several sites may be combined based on some common trait to form a quasi-center, which is administered by a single investigator.

Centers, in a multi-center study, are conducted under the same protocol, and are generally geographically separated and are independently administered.

Now, in many of my slides, I will use the abbreviations LOCF and OC, meaning last observation carried forward, and observed cases.

I also will use the term N points, which refers to the last response recorded for a patient or the final LOCF value.

Observed cases refers to all the data observed at a specific measurement time. This should not be confused with completer data, which is the database of patients who have completed the study.

Also, to avoid any confusion, I would like to point out that the sponsor may use the term, visit-wise, and this term is synonymous with observed cases.

Now, all the doses in this submission were reported as mean model doses. The mode for each patient during a single week was found and the mean of these model doses is computed to summarize weekly dosing.

I was initially concerned with the use of mean modal doses instead of mean dose, because it seemed like the mode might overestimate the dose taken by patient, since it would ignore missed doses.

However, a comparison of mean dose versus mean model dose showed no appreciable differences, with differences generally less than five milligrams.

Listed on this slide are the eight randomized, double blind placebo controlled trials I

will be discussing today.

With the exception of CN 104-002, these studies are listed in the order that they were conducted. Study CN 104-002 was conducted before the last two CN studies.

All the studies were conducted either at multiple sites or at multiple centers, and centers were geographically disbursed throughout the U.S. and Canada.

The first six studies were six-week studies, while CN 104-005 and 006 were eight-week studies. With the exception of the one fixed-dose study, study 0007, these studies were all titration studies.

I have broken the studies into three groups -- low, high/low, and high. The low dose studies utilized only nefazodone doses of 300 milligrams per day or less. For the three high/low studies, two dose levels were used. And for the two high dose studies, the peak allowable dose was 600 milligrams per day.

The plus preceding the study numbers indicates those trials that had an active control arm of Imipramine in addition to the placebo arm.

Before I go on to the next slide, I want

to point out that I usually will refer to these studies by only the last digit of the study number.

Following a baseline wash-out period ranging from four days to four weeks, patients were randomized to treatment if they were diagnosed as exhibiting major depression based on research diagnostic criteria in the three early studies, and on the DSM-III criteria in the later studies, and also if they had a HAM-D 17 total of 20 or greater.

Four variables I focused on for my review are listed here -- the HAM-D 17 item total, the depressed mood item, which is measured on a scale of 0 to 4, the two CGI scores -- severity of illness and global improvement, which are both measured on a scale of 1 to 7.

The first three variables were evaluated as change from baseline, and in all of the studies, only the intent-to-treat data was analyzed.

In my presentation, I will primarily emphasize the HAM-D total results.

In the majority of the efficacy studies, about two-thirds of the patients were women. The average age was about 39 years and more than 85 percent of the patients were Caucasian.

With respect to demographics, there were

no major treatment group imbalances at baseline in any of the studies.

In addition, treatment groups had comparable psychiatric history. About half the cases presented with recurrent depression. And the median number of prior depressive episodes in these studies was one.

For those instances where treatment groups differed on baseline values for the efficacy variables, an analysis of covariants, or a stratified Cochran-Mantle-Hanson procedure was performed to adjust for these baseline differences.

Now, I am going to start my presentation of the efficacy trials with the three trials that have treatment arms for both low and high dose nefazodone, to show you the relationship between those dose levels.

Then I will show you the results from the studies of just the low dose nefazodone. This discussion of low dose, then, will be followed by a discussion of the high dose.

The three trials in which patients could be randomized to receive either a low dose or a high dose of nefazodone were studies 003, 004A and 004B.

In study 003, patients in the low dose

nefazodone group could be titrated to a peak dose of 250 milligrams per day, and in the high group, to a dose of 500 milligrams per day, while in studies 004A and 004B, higher peak doses of 300 and 600 milligrams per day were allowed.

Note that only study 003 had an Imipramine arm. Study 003 was originally designed as a five center study. One center withdrew from the study without enrolling any patients.

Three centers enrolled patients and then stopped after one to eight months for a variety of reasons, including slow enrollment, change in personnel, or change in priorities.

Those three centers enrolled a total of 24 patients. Sixteen of those patients completed the study.

The protocol was amended to increase enrollment in the one remaining center, center 2191. One hundred and eighty patients were enrolled in that center.

For my presentation, I will focus primarily on the one large center, but I will mention the results for the small centers combined with the large centers for comparison.

My analysis of all the data were not

stratified by center, primarily due to the disparity in the sizes of the centers. It did not seem sensible to me to give the results of a center where 88 percent of the patients' equal weight, with the remaining three small centers having the remaining 12 percent of the patients.

So, when I refer to the all patients analysis of study 003, I am referring to an analysis which gives equal weight to each patient.

Studies 004A and 004B were both two-center studies conducted under the same protocol. Each study enrolled 80 patients into each treatment arm.

These two graphs depict the mean change from baseline on the HAM-D total for each of the three high/low studies at week six. The results to the left are the last observation carried forward results, and to the right we see the observed cases results.

In the red squares are the Imipramine response. The open boxes are the placebo responses, and the green dots are the low dose. And the triangles, the dark triangles, are the high dose nefazodone.

If you look first at the results for

completers, which are these results here, and focus just on the placebo and low dose responses, you see that the magnitude of the low dose response is either equivalent to placebo or smaller than placebo.

Looking now at the last observation carried forward data for studies 004A and 004B, no difference exists between the low dose and placebo. The response for high dose for 004B, however, is significantly greater than placebo.

In study 003, there appears to be ordering of effects among the treatment groups.

Now, the next two slides I will present the HAM-D results plotted over time for these three studies.

To the left are the results from the study 004A, and these are both graphs of the last observation carried forward data. The observed cases data look very similar for these two studies. And to the right are the results for 004B.

The top dotted line is the placebo response. And the green dotted line is the low dose nefazodone, and the solid line is high dose nefazodone.

Note that there is no significant

difference between the low dose and placebo for the duration of the trials, not just at week six.

In addition to both 004A and 004B, the low dose was not statistically different from placebo for any of the other efficacy variables.

I would like to stress here that an Imipramine arm would have been helpful, particularly in 004A, where no treatment differences are seen.

In this graph, the red line here is the Imipramine response, again the solid line is the high dose, and the green dotted line is the low dose. And this top line is the placebo response.

Note for study 003, that last observation carried forward, and observed cases graphs look quite different. Later, I will talk about the LOCF OC differences you see here for the high dose, and the relationship of the drop out patterns for this difference.

For now, though, I would like you to just focus on the relationship between the low and high dose responses.

Note that up to week four, the two nefazodone groups look quite similar. At week four, about 80 percent of the nefazodone patients, and 64 percent of the placebo patients were still on study.

I performed a repeated measures analysis using the last observation carried forward data from all six weeks, to compare the low dose to placebo, and the results were non-significant with a P value of .21. Adding in the patients from the discontinued centers increased that P value.

Now I would like you to look at weeks five and six. The LOCF responses appear to be ordered at these two groups. And at these last two weeks the high dose is significantly different from placebo, but the low dose group is not.

This relationship between the high dose, low dose and placebo, is also apparent from the other three efficacy variables. But again, the paralyzed comparisons of placebo to low dose were not significant.

Next, I would like to show you the results for the low dose studies, CN 104-002. The relationships among the results of the three treatment arms in this study look similar to what we just saw in study three.

The three treatment arms in study two were low dose, Imipramine and placebo. Patients randomized to either nefazodone or Imipramine could be titrated to a peak dose of 300 milligrams per

day.

A hundred and eighty patients were enrolled at three sites in San Diego and all sites were administered by Dr. Feighner.

Seventy-seven percent of the nefazodone patients completed the study, while 63 percent of the placebo patients completed. Most of the drop-outs in the placebo groups occurred during weeks one, three, and four, primarily due to patient withdrawal of consent or lack of efficacy.

Ten percent of the low dose patients dropped due to lack of efficacy, and none due to adverse experience, while 18 percent of the Imipramine patients dropped due to an adverse experience, with most of those occurring during the first week.

To the left is a graph of the last observation carried forward means, and to the right, the graph of the observed cases means.

Again, the color scheme is the same. The lower red line is the Imipramine group. And then we have the low dose and the placebo group.

Looking just at the week six means, neither of the observed cases nor the last observation carried forward low dose means are

statistically significantly different from placebo. However, the last observation carried forward comparison is close to significant with a P value of .08.

The Imipramine placebo comparisons were significant at every time point after week one, from both the last observation carried forward data and the observed cases data, while the low dose data was only significantly different from placebo at week five in last observation carried forward.

The results for the other three efficacy variables were consistent with the HAM-D total results, in that the LOCF and the OC nefazodone and placebo comparisons did not agree. And the magnitude of the low dose response was consistently larger than placebo, but less than Imipramine.

But, unlike the HAM-D 17, the P values for the nefazodone and placebo comparisons, at week six, with the last observation carried forward, for all three variables it was less than or equal to .05. However, the observed cases comparisons were not significant.

The next study we will look at will be the fixed dose study. Among the eight placebo controlled trials, this was the second study

conducted by the sponsor. It was completed about three years before the high dose studies.

Patients were randomized to placebo or a fixed dose of 50, 100, or 300 milligrams per day of nefazodone.

Of the 194 patients enrolled at a total of five centers, more than 60 percent completed the study in each treatment group.

There were about 30 patients in each treatment group at the end of the study. Major reasons for drop outs in this study, the major reason was lack of efficacy, with about 12 percent of the patients dropping for that reason.

Drop-outs for adverse events were primarily seen in the two highest doses, with 11 percent of the 200 milligram patients dropping and 19 percent of the 300 milligram patients dropping for that reason.

Now, unlike the last graphs we looked at, here you should note the similarity between the last observation carried forward and the observed cases graphs.

Also note that it is difficult to differentiate the different doses of nefazodone. I will try to point them out here. This upper line is

the placebo response, the dotted line is the 300 milligram response. This lower line is the 200 milligram response. This pink line or whatever color that is, is the 50 milligram dose. And then, the triangles represent the 100 milligram dose.

At week six, for both LOCF and OC, only the 200 milligram group's response is significantly different from placebo. Neither the 200 milligram group nor the 300 milligram group results were significantly different from placebo for the depressed mood item or for the CGI scores.

In fact, only the 50 and 100 milligram doses showed some significant placebo differences on these other three efficacy variables, and that was at week four and five.

The observed cases, week five, HAM-D totals, these responses were interesting in that all the doses except the 300 milligram dose were significantly different from placebo.

I investigated the 300 milligram data carefully to determine if the blip you see there that was seen at week five was due to a few outliers.

I found that one-fourth of the patients who had data at weeks four, five and six showed the

pattern that you see here. That is, they showed an increase in the HAM-D total at week five.

Clearly, I think the fixed dose study revealed no relationship between dose and response in these lower doses under 300 milligrams or equal to 300 milligrams a day.

Now, these graphs summarize the responses for low dose nefazodone. Again, you have the same -- these are the placebo responses, the open scores, just like we saw in the earlier scatter plots. And the green dots are the low dose. I did not plot the high dose on this graph, maybe to make it a little less confusing, I guess.

And the Imipramine are the red squares. Do not confuse these points with Imipramine. These are doses below 200 milligrams. In study 007, this point represents the 200 milligram response as well as this down here.

Now, this study, 0045, I have not discussed yet. This was the first placebo controlled study conducted by the sponsor. And the mean modal dose of nefazodone in the last week of the study is 175 milligrams per day, indeed a very low dose.

So, as you can see, the nefazodone is

not discernible from placebo.

To focus just on the observed cases graph which is in these points here, note that the only mean, in addition to the Imipramine, which is different from placebo, is the 300 milligram dose in the fixed dose study.

So, the computer data reveals no important differences between low dose nefazodone and placebo.

The last, I boxed in the results from study three and two, that showed some ordering of the treatment effects, perhaps suggesting that some activity in the low dose was clearly not providing significant benefit over placebo.

Okay, now we will go on to the high dose studies. These are the five studies that we will be looking at. The first three we have already talked about with respect to the low dose.

Remember, these studies were all six week studies, which included both the low and the high dose arm.

Now, the last two studies, studies 005 and 006, were eight-week studies with three treatment arms -- placebo, Imipramine and high dose nefazodone.

This slide shows the baseline means for the HAM-D 17 total of the depressed mood items, and the CGI severity of illness score for high dose nefazodone, placebo and Imipramine.

A 3 on the HAM-D depressed mood items indicates from moderate or depressed mood and obvious behavioral evidence.

A CGI severity of illness score of 4 denotes moderately ill, while a 5 denotes markedly ill. You can see that the groups were quite comparable.

The reason that the Imipramine response is higher is because this -- remember, Imipramine was not in two of the trials. In the two trials that Imipramine was not in, the baseline for the CGI severity was about 4.3.

Now, this slide is to remind you that study three was essentially a single center study. Again, I will focus primarily on results from studies for center 2191, but I will mention, as I did for the low dose, what the results were when the 24 patients in the other three centers were included in the all patients analysis.

Note here that the peak allowable dose of nefazodone was 500 milligrams per day, while in the other four studies, the peak allowable dose is

600 milligrams per day.

This graph shows the percentage of patients who completed each week of the study. The open squares are the placebos and the Imipramine is represented by red, low dose by green, and the solid line is the high dose.

Most of the drop outs in the placebo and Imipramine groups occurred during week three. Seventy-five percent of the high dose nefazodone patients completed the study, while only 53 percent of the placebo patients were completers.

This pattern of drop outs for the placebo and nefazodone group is not unusual for this NDA. What is unusual is that in the Imipramine group, most of the drop outs occurred during week three, while ordinarily in antidepressant trials, Imipramine patients drop predominantly during groups one and two, due to adverse events.

However, in this study, most of the drop outs in all the groups were due to lack of efficacy, as you will see in the next slide.

About twice as many placebo and Imipramine patients due to lack of efficacy than the nefazodone patients.

It is interesting that very few patients

in the drug groups dropped due to adverse experiences, none in the high dose nefazodone group.

You have seen this graph before, so this time I have removed the low dose group so that the relationship between the high dose group and placebo group is more clearly discernible.

Looking at the last observation carried forward means over time -- and that is the graph to your left -- it is clear that both nefazodone and Imipramine meet placebo. At week six, the P value for the nefazodone placebo comparison was .03. An all patients analysis of covariants yielded a P value of .05.

For the observed cases results at week six, nefazodone is not significantly different from placebo, with a P value of .5.

To examine the observed cases results further, I performed a repeated measures analysis, using the completer data to compare nefazodone to placebo. Including the data for weeks one to six produced a P value of .03. For the all cases analysis, the P value was .07.

If I just included the last three weeks, this comparison was not significant, with a P value of .19.

The sponsor performed an unbalanced repeated measures analysis using all the observed cases data, which yielded a P value of .07 for the placebo/nefazodone comparison.

These repeated measures results are more favorable, and obviously agree more closely with the last observation carried forward analysis than the fixed results alone.

Now, in addition to these further analyses of the observed cases data, we were interested in examining the role drop outs play in the last observation carried forward outcome.

I found that excluding all patients that dropped out during week three rendered the last observation carried forward week six analysis non-significant with a P value of .21.

I looked at the means for these drop outs and found that the placebo patients showed a small mean increase on the HAM-D, while the nefazodone patients showed a decrease of about 4.

Looking at the means of the patients still on study at week three, the placebo patients had a mean of 06.4 and the nefazodone patients a mean of 08.

So, not including the placebo drop outs

clearly biases the results against the drug, producing the non-significant results we see at week six for the observed cases.

However, the draw back to including the last observation carried forward data for drop outs is that we must assume that these patients would not change if they remained on study.

We decided to try another approach, which allows one to compare the slopes of the treatment groups. In this way, all the data is used, not just the last observation carried forward data, or not just the observed cases data, as in the repeated measures analysis.

Using the approaches of Liang and Zeger, and of Wu and Caroll, Dr. Tagauchi(?) of the FDA's division of biometrics found a significant difference between high dose nefazodone and placebo. The P value for that analysis was .02.

These are the week six results for the other variables that were measured. What we see here is basically what we saw for the HAM-D total. The last observation carried forward comparisons are significant, while the observed cases comparisons at week six are not.

Again, the Imipramine observed cases

responses are larger than the nefazodone responses.

Now we will go on to study 004A. You recall that study 004A was a high/low study with no active control arm. Two hundred and forty patients were entered in this study, 80 patients in each treatment group.

Approximately 60 percent of the patients completed the six weeks of treatment. Eighteen percent of the high dose nefazodone patients dropped due to adverse events, while the same percentage of placebo patients dropped due to lack of efficacy.

At week six, the high dose group was not significantly different from placebo on any efficacy variables. In addition, for the observed cases data, the magnitude of the placebo response was greater than the nefazodone response.

Now as I did for the last study, I have removed the low dose arm from the graph. Basically what you see here is no difference between the groups at any measurement point.

At week four, about 70 percent of the patients remain on study in all the groups, and we see that for both the observed cases and the LOCF, neither is significant.

Also, the efficacy results were not

positive on any of the other efficacy variables.

The Imipramine group here may have helped us ascertain whether it was the test situation that failed or whether it was, indeed, the drug that failed.

We will go on to 004B. Study 004B was conducted under the same protocol as under study 004A. As in study 004A, two centers participated in study 004B. Eighty patients were randomized to each of the three treatment arms, high, low and placebo.

The percentage of patients completing this study was the highest among all eight studies. Seventy-five percent of the low dose patients completed, 79 percent of the high dose, and 73 percent of the placebo patients.

Fourteen percent of the patients in the high dose group and 14 percent in the placebo group discontinued treatment due to adverse events. It is unusual to have that many placebo patients discontinue for adverse events.

Few patients dropped due to lack of efficacy in any of the groups. Only four placebo patients and two high dose patients dropped for that reason.

Here I am just showing you the last

observation carried forward graph, since the observed cases graph was essentially the same.

The placebo and high dose groups are clearly different. These differences were statistically significant from week three through week six.

This slide shows you the results for the total of the depressed mood item and the two CGI scores. What stands out on this slide is the lack of efficacy on the HAM-D depressed mood items.

An analysis stratifying it on baseline yielded a smaller P value, .14. Nevertheless, the P value is still non-significant.

This is interesting, since the HAM-D total treatment different of 3.2 is significant, and the value, too, is consistent with the differences observed in the other trials.

Since the HAM-D depressed mood item appears to be not contributing substantially to the HAM-D total treatment difference, I was interested in knowing which items were contributing to this difference.

This is a rather busy bar chart, but this chart shows the six items -- depressed mood, guilty feelings, suicide, work and interest, psychic

and somatic anxiety, and anersia -- which contributed the most to the HAM-D total treatment difference observed in 004B.

These six items, combined, explain about 60 percent of the treatment difference observed on the HAM-D total. Each bar represents the percentage of the HAM-D total treatment difference which is explained by each of the items. I am just repeating that, just so that you understand.

For example, the depressed mood item for 004B, which is the red bar, comprises about six percent of the HAM-D total treatment differences.

Now, in addition to study 004B, I have included the results from the four other centers, which showed positive results on the HAM-D totals. But first, I would like you to focus on the solid red bars, the results from 004B.

Note the items that contribute the most to the HAM-D total treatment difference are work and interests, suicide, and guilty feelings.

When we factored in the placebo comparisons for both suicide and work and interest, it was statistically significant.

I included the other studies on this graph, not just to make this a busy graph, but

because I wanted to see if the items that showed the large differences in study 004B also showed large differences in these other studies that showed causative changes on the HAM-D total and on the depressed mood item.

Inconsistencies may have suggested that the 004B patient sample was inherently different from the patient samples of the other samples. This, however, does not seem to be the case.

We see that work and interest, these four middle bars, in particular, and the other items as well make up a large percentage of the HAM-D total treatment difference in these other studies, as well as in study 004B.

Going on to study 005, study 005 was composed of two kind of quasi-centers. Center one was composed of six psychiatric sites, and center two was composed of seven family practice sites.

The protocol stated that the treatment sites would include both psychiatric and family practice sites, but did not specifically state that one type would be defined as a center. However, randomization was blocked on center, implying that assignment of sites was made a priori.

There were three treatment arms -- high

dose nefazodone, Imipramine, and placebo. High dose patients could be titrated to a peak dose of 600 milligrams per day. Note that this study was an eight-week study, two weeks longer than the others that we have discussed.

This slide shows the number of patients randomized and completing in each center. At week four, in both centers, about 70 percent of the patients remained on study.

It is interesting to note, in center one, that more patients in the placebo group completed the study than in either of the drug treatment groups, while in center two about 20 percent more nefazodone patients completed than in the other groups.

In those centers, the major reasons for drop out in the nefazodone group were adverse experiences and loss to follow up. No nefazodone patients in center two dropped due to lack of efficacy, while four in center one dropped for that reason.

The major reason for drop out in the placebo group was lack of efficacy, in both centers, with most of those drop outs occurring after week four.

In center one, 18 percent of the Imipramine patients dropped due to adverse events, primarily during the first three weeks. An additional 18 percent dropped due to lack of efficacy in the Imipramine group, primarily during the last five weeks of the study.

In center two, no Imipramine patients dropped due to lack of efficacy, while 26 percent dropped due to an adverse experience.

These graphs depict the LOCF means for each center. The observed cases result looked similar to the last observation carried forward results.

I am presenting the results by center, even though this is not the approach we ordinarily take. Generally, in a multi-center study, we are primarily interested in the overall treatment effects. However, routinely, we check center results for consistency, particularly if the P value for the treatment center interaction was less than about .2.

In this study, the P value for interaction was less than .02, strongly suggesting the by-center results should be explored.

In addition, one could argue that the patient populations for these centers may be

inherently different, since one was conducted at only psychiatric sites and the other only at family practice sites.

First, I would like you to focus on the placebo groups for each center. And the placebo response is this lower dotted line for center one. And for center two, it is the upper dotted line.

You see that the placebo response in center two is appreciably smaller than the placebo response in center one. The change from baseline at week eight in center two is only about 4. In the other studies in this NDA, the mean placebo change was about 7 to 9.

Second, notice that the drug effects in both centers look about the same. And focus primarily on the high dose and you can see that, in fact, this was a larger drop in center one.

So, the nefazodone/placebo comparisons for center two were highly significant with P values less than .01, while neither nefazodone nor Imipramine were different from placebo in center one.

The lack of an Imipramine response without explanation is another reason to look at study 005's results by center. It is comforting,

however, that the results for both centers combined were still statistically significant. The P value at week eight was less than .01.

The results for the other three efficacy variables are consistent with the HAM-D results. Again, in center one, the large placebo response renders the comparisons non-significant, while in center two, all the comparisons are significant at P values less than .01.

What is interesting to note on this slide is the fact that the responses for nefazodone is greater in center one than in center two.

Now we will go on to the last study I will be discussing this morning, which is study 006.

Study 006 has the same design as study 005. The two centers enrolled a total of 135 patients, about 45 patients in each treatment arm.

These graphs show the percentage of patients remaining on study by week for each center. I am sure it is immediately obvious to you why I am presenting this data to you by center.

As you can see, the drop out patterns observed in center one, were very different from the patterns seen in center two.

Looking at center one, you note that

about 20 percent of the placebo and Imipramine patients drop out during week one. About another 20 percent drop during week three. Only 35 percent of the nefazodone patients completed the study and only 41 percent of the Imipramine and placebo patients were completers, whereas in center two, more than 65 percent of nefazodone and placebo patients complete the study.

It is interesting to note that in center two, about 20 percent of the nefazodone and Imipramine patients dropped during week one, primarily due to adverse events.

Since there were so many drop outs in center one, I wanted to show you the reasons for drop out. What is particularly interesting here is the high number of patients who withdrew consent.

Usually very few patients withdraw consent in these studies. Those patients dropped, primarily, during week one.

There are also a surprising number of patients that dropped due to lack of efficacy in the nefazodone group, 22 percent.

By contrast, only one patient in the nefazodone group of center two dropped due to lack of efficacy.

In center two, the main reason for drop out was adverse experience. Sixteen percent of the nefazodone patients in center two, and twelve percent of the placebo patients, and twenty-four percent of the Imipramine patients withdrew due to an adverse experience.

For study six, the results at week eight, last observation carried forward, with the centers combined, were non-significant, with a level of significance of .35.

The P value for the center by treatment interaction with Imipramine in the model was .26. When I dropped Imipramine from the model, the interaction turn was significant at a .15 level.

The latter P value, plus the differential drop out pattern, suggested the result for each center should be looked at separately, at least in an exploratory manner.

It is clear from this graph of center one, that neither nefazodone nor Imipramine are different from placebo. In fact, the placebo response shows a slightly larger drop from baseline in the HAM-D total than the two drug groups. The fact that Imipramine does so clearly in center one is another reason to look at the centers separately.

For center two, nefazodone and Imipramine are not distinguishable. However, the Imipramine placebo comparison at week eight, last observation carried forward, is statistically significant with a P value of .03, while the nefazodone/placebo comparison is borderline significant with a P value of .09.

The observed cases results for nefazodone were also borderline significant with a P value of .07.

This table shows the nefazodone/placebo, last observation carried forward, treatment differences for the depressed mood items and the CGI for center two only. These comparisons were all non-significant for center one.

Only the CGI severity score P value is greater than .05 at week eight. The observed cases comparison for that variable, as well as the other two variables, were all statistically significant.

On my next slide, I am going to summarize the high dose, HAM-D 17 total data, from these studies we have just discussed.

This is a plot of the change from baseline mean at end point for the five high dose studies. In your package you also have a plot of

the six week mean.

Since for studies 005 and 006, the week 6 and the week 8 means look very similar, I am presenting here only the end point mean. Remember that the X axis are the studies that we are talking about, study 003, 004A, 004B, center one of study 006, center two of study 006, center one of study 005 and center two of study 005.

The boxed responses are those studies or centers showing positive results from nefazodone over placebo on the HAM-D total at end point.

With the exception of study 004A and center one of study 006, the nefazodone response is quite consistent. Those are the dark triangles. These values range from about -11 down to -13.

The results for center one of study 005 and center one of study 006 fail to distinguish nefazodone as well as Imipramine from placebo. Notice that the lack of an Imipramine arm for study 004A creates problems in the anticipation of the study results.

On the next slide, I will point to you the dosing for 004A, which may offer some explanation for the lack of a difference here.

This is my last slide and it is a pretty

busy one. The solid green lines are those centers or studies that showed a positive effect on the HAM-D total.

Notice that the Y axis is the mean modal dose and the X axis are the weeks on study.

This is the mean modal dose for the patients on study. So, we can think of it as the observed cases modal dose at each week for each of the centers.

My goal with this graph is to try to identify some pattern between the positive results on the HAM-D and the dosing regimen.

I will point out some of the studies that I would like you to pay attention to. This J represents study 005. Notice the like letters refer to centers from within study. So, this is center two and this is center one from study 005.

And for study 003, notice that the dosing levels off in study 003. The protocol specified that they should reach their peak dose around week two or three -- I don't remember it exactly -- and remain at that dose for the remainder of the study. And as you can see, it pretty well does that.

Study 004B, I also want to point out,

this was also high dosing in study in 004B, just as it was in study 003. Notice 004A is this upper line here. 004A, remember, was the study that showed no differences.

Basically, I think this slide says that the dosing seems to range between 200 and 500 and does not really pin down any dosing range that we might recommend.

This is my last slide, so I would be happy to answer any questions that you might have at this point.

DR. TAMMINGA: Thank you very much for your detailed presentation. I would suggest that we ask whatever questions we want to Ms. Mele's presentation, but save the discussion until a bit later.

DR. LAUGHREN: Joy, just one point of clarification. On study 003 where you used the repeated measures approach and the longitudinal data analysis approach for the observed cases data for HAM-D total, that level is fairly persuasive. I wondered if you did that for any of the other variables.

MS. MELE: No, we did not. We didn't have time to do that. But the other variables did

follow the same pattern, so we might expect that it might have the same results. Remember, the other variables are categorical, too, which presents some problems.

DR. CHARNEY: In relation to your last slide, was there any correlation between final dose and treatment response in terms of HAM-D or any depression item.

MS. MELE: We didn't do a formal analysis of the correlation between the two, but I did look at them and, in my overview, I think there is a bar graph showing the relationship between the last -- do you know what page it is on.

DR. LAUGHREN: It is on page 47.

MS. MELE: On page 47 of my review. And just looking at that data, there seemed to be no relationship. I didn't do any formal analysis of that, however.

DR. TEMPLE: Can you give any insight into how some of the dosing arrangements worked out. Some of the supposed high dose studies didn't even get doses up beyond 300, which is what the low dose was seeking. What was the dosing paradigm. How did they decide. Why didn't they go higher, things like that.

MS. MELE: I will make a few comments and then I will ask the company to fill in. But the studies did vary, first of all, in the starting dose that was used. And then, for instance, in study 005 it started at 100 milligrams a day -- is that right -- and then we continued -- we could go up to 200 milligrams and then they had to remain at 200 milligrams for three weeks, and then it could increase, whereas in some of the other studies, they started at 100 milligrams but they could immediately increase the dosing in the second week. So, that is one difference and perhaps it can explain some further differences between the study.

DR. ROBINSON: I can try to explain the differences. We really studied not only with emphasis on efficacy but trying to establish the therapeutic dose range.

So, in the initial two dose range of the study, we asked the investigators to raise the dose rather rapidly in the first and second weeks, in order to try to bracket the dose range of interest for later studies.

So, there were differences in the location of studies, even with the same design.

The early two dose ranging studies was

essentially to give us information that would be helpful to us in designing the later studies. I don't know if that answers your question or not.

DR. TEMPLE: Well, not entirely. I guess I remain somewhat mystified as to how doses were chosen. There is major non-linearity that would confuse even the most careful work-up. And I guess I can't tell how you figure out where you are under those circumstances. A small change in dose leads to a large change in blood level.

The dose and time must be confounded in ways that remain mysterious. You don't have some blood level data hidden away anywhere that we are going to hear about or anything, do you.

DR. ROBINSON: Yes, there was blood level data submitted. Unfortunately, we felt it was only useful with 100 or so patients. It appeared that there was a wide range of blood levels. We focused on those six to eight hours after dosing.

There was possibly a non-linear relationship of plasma levels, but it did not appear to be useful or predictively useful.

DR. LEBER: I think this really is a follow up on Dr. Temple's question. I think in a concrete way, if you were to look at Dr. Mele's last

slide, can you put it up.

(Slide is shown.)

DR. LEBER: If I have it right, look at the difference between 004A obtained doses, which represent the open circles, which is the totally failed trial, which allowed 600 dosing in the high arm, and 006-2, which are the closed triangles on mine but I think it is H.

Both of them are designed to bring a treatment arm to a dose of 600 milligrams and I think that was the question that I believe Dr. Temple was asking. How is it that the same assigned dosing pattern leads to such discrepancies in achieved dose.

MS. MELE: What I remember from 004A and 004B, and correct me if I am wrong, they could start at a dose of 200 milligrams per day. In fixed they started at a lower dose, 100 milligrams.

So, by the time even week one came, that was the first couple of days, you start at a dose of 200. They already look different. Is that true.

DR. ROBINSON: That is correct. The active and placebo controlled studies, the dose interaction is done weekly. And so, the dose tended to be considerably lower during the first week of

treatment, more gradual.

DR. CHARNEY: This is also related to dosing. If you look at it within study 005 and 006, the two centers differ quite a bit.

MS. MELE: I did point those out. Study 006 has a sort of positive center at center two, and this H here represents center one. Now, in 005 -- again, I am recalling this so if I am saying something wrong the company can correct me -- but the protocol is amended in study 005 after about 94 patients had entered the trial.

A larger percentage of those 94 patients came from center one, which is here. And the amendment called for a slowing down of the titration. So, that may be what is reflected here, those differences in those two centers. I don't know if the company has any further information on that, whether the changing or the protocol amendment contributes to the difference that you might see between center one and two.

DR. ROBINSON: Yes, of course, we did look at that and it was our belief that that does explain some of the difference between center one and center two.

As we gained information from the

completing studies, we had more experience with those, and it was our opinion that it was important to follow those strategies in later studies with active and placebo controls that we had done with study 005 and also 006.

DR. FRANK: Could you say something about the initial dose and titration strategy for the Imipramine control. Was it in the same in each of the trials, did it differ by trial. Let me just ask those two questions first.

MS. MELE: It differ and I don't recall the exact details on that. So, again, I will ask Dr. Robinson, do you recall whether the Imipramine -- I do remember that their initial doses did vary, as they did for nefazodone, but I don't recall the exact numbers.

DR. ROBINSON: I am not sure I understand your question.

MS. MELE: The starting dose.

DR. FRANK: Let me say where I am going to and that is, my question is whether it has any relationship to drop out in the Imipramine control subjects. In other words, how high were they started and how fast were they titrated up.

DR. ROBINSON: They tended to be started

at 100 milligrams corresponding to 200 milligrams of nefazodone. In the first group, they received on average 100 milligrams of Imipramine, 200 of nefazodone with titration in the later studies, it would graduate after a week.

DR. HAMER: My perception, after staring at this material for a while, is that there seemed to be a larger placebo effect asserted in many of these studies than I would have sort of ordinarily expected in similar studies.

I don't recall from the material that we were given, whether there was any provision in terms of the inclusion/exclusion material to eliminate subjects who had a large response during a wash-out period. Was there a wash-out period.

MS. MELE: There was a wash-out period. I mentioned that in the beginning, and it ranged anywhere from four days to four weeks. There was a great deal of variability among these studies. Tony, do you want to make a few comments about that.

DR. LAUGHREN: Only a general comment. I think there is sort of a building consensus, from looking at a lot of data on placebo wash-out, that placebo wash-out in depression studies doesn't work very well, that you don't get the placebo response

until after you randomize patients.

DR. HAMER: I guess my question still remains. Was there an exclusion criterion that said if subjects responded, that they should --

MS. MELE: Yes.

DR. TAMMINGA: And in addition, we will get a whole presentation from the company in a little bit with an opportunity to ask them direct questions, too.

DR. CASPER: My question also refers to the Imipramine data, and I wonder if you have plotted similar data for Imipramine.

MS. MELE: For the doses.

DR. CASPER: For the doses, yes. So, here if we have the low dose at 300 milligrams and the high dose is 600 milligrams, most patients reached a dose of 475, perhaps, in the high dose.

And the question would really be whether the Imipramine patients reached, invariably, a dose of 300 milligrams, which would be a very high dose of Imipramine, which might explain the high drop out for adverse effects in the Imipramine group.

MS. MELE: If you look in the summary, I did not do a graph, first of all, of the Imipramine doses, but I did summarize the Imipramine doses in

my summary table which is on page 51 of my review.

What I think you can see from this table -- this is just the high dose studies -- if you look to summary table three, you will see some of the other studies.

What I have summarized here, this is the peak dose, the last dose for the Imipramine group, for the observed cases. So, that is the last week on study. The fifth column is the Imipramine modal dose.

So, you can see the doses range from about 140 to about 220 at the end of the studies.

DR. HEZEL: Can you tell me what the final number of patients who appear to have a positive effect is.

MS. MELE: No.

DR. TAMMINGA: I bet the drug company could. We will let them incorporate that into their presentation, the final number of positive responders.

MS. MELE: Defined how. How would you define that, the final number of patients in the positive centers, or do you mean actually the patients who showed positive response.

DR. HEZEL: Well, I would look at it

both ways.

DR. LEBER: Well, this is almost an editorial point, but I will ask it as a question. We have not done an analysis that examines, within study, individual patients' change scores on the HAM-D versus the retained modal doses by time, have we.

MS. MELE: No.

DR. LEBER: Because I think the editorial point, of course, is that by looking at the study mean doses, it is like looking at any mean. It obscures the differences that are probably attributable to individual response, so that this data doesn't really speak to dose response in the sense we ordinarily mean it.

DR. TEMPLE: The only thought I had is that where the placebo groups respond quite dramatically also, the number of patients who respond is going to be somewhat confusing, because in the failed studies it is because everybody responded.

One could certainly do responder analysis by setting criteria change of this magnitude or that magnitude, and compare those.

MS. MELE: The company did look at it

responder/non-responder.

DR. CHARNEY: I think if the company could address these points in particular, because if you look within study 005 and study 006, the centers that had positive results had lower final doses.

DR. TAMMINGA: I am sure the company will speak to that.

DR. CHARNEY: And those low doses are not that far from the final doses in the low dose studies. They are only separated by about 50 or 60 milligrams.

DR. TEMPLE: Just one last, I guess, also editorial thought, and that is, titration studies typically produce things like inverted U-shaped dose response curves, because the people who are resistant and don't respond very well tend to be the ones that get titrated up.

It is not the right way to discover dose response relationships. The parallel study is. It was at least somewhat disappointing to me to see that that early study was never followed up later once the larger needed dose was needed, because it is very hard to deduce dose response in this setting.

DR. TAMMINGA: Pharmaceutical companies

must be ready to throw clinicians' dosing judgment out of the window when you look at data like these.

DR. TEMPLE: Well, in many areas, that lesson has been well learned and you don't -- there are ways of extracting dose response information, but you can't just look at the response and the dose. You have to use complicated models of analysis that I can only refer to, but don't understand.

But certainly, they have been successful in hypertension in teasing dose response relationships out of these kinds of data, sometimes anyway.

DR. TAMMINGA: Unless there is further comment, we will thank Ms. Mele for her very detailed presentation and will go on to the safety review by Dr. Hearst.

Agenda Item: FDA Presentation - Safety Review.

DR. HEARST: In my presentation, I am going to characterize the safety profile of nefazodone. I will be talking, first briefly, to give an overview of the clinical pharmacology of nefazodone.

Secondly, I will be describing the data

sources that contributed to my review. Finally, I will describe the actual safety findings.

Nefazodone is a new compound synthesized by Bristol-Meyers. It is a chemical and pharmacologic analog of triazodone and a member of the phenylpiperazine class of antidepressants.

Its proposed use is as an antidepressant. Its presumed mechanism of action is 5 HT2 antagonism and serotonin re-uptake in addition.

Other actions are a weak alpha one adrenergic antagonism and norepinephrine uptake inhibition, at least in vitro.

Nefazodone is rapidly and completely absorbed with a T max of one hour. Its absolute bioavailability is between 15 and 23 percent. It is approximately 99 percent protein bound. Nefazodone does not alter in vitro protein binding of many other protein bound drugs.

The total recovery is about 85 percent, with 55 percent found in the urine, 30 percent in the feces. It has extensive presystemic metabolism.

We cannot concentrate on nefazodone alone. There are a number of metabolites and the better characterized ones are identified in this

column.

The ratio of these metabolites to nefazodone is listed in the second column. This is area under the curve at steady state. The half lives are listed in the third column.

A note on the dione, even though it sticks around a long time and is present in fairly great quantities, its activity is only about one-sixth of nefazodone at the 5 HT2 site.

There are non-linear pharmacokinetics for nefazodone and hydroxynefazodone. By that, I mean an increase in the dose results in a disproportionate increase in the plasma concentration.

There are also food effects with an absorption delay and a 20 percent decrease in bioavailability. The clinical significance of this is not known.

Special populations were looked at. Elderly females show higher plasma concentrations than elderly males. Elderly females also show higher plasma concentrations than young females. Renally impaired patients have essentially normal clearance, but caution would appear to be advisable.

Hepatically impaired patients show

decreased clearance for both nefazodone and hydroxynefazodone, with the AUC being 20 percent higher.

The integrated safety database used throughout the majority of my review is composed of 2,256 nefazodone treated patients in Phase II, III trials, and 424 patients, or subjects, in Phase I trials. Corresponding numbers for the other treatment groups are listed.

This slide describes the demographic profile for the Phase II, III studies. The Ns are listed below each treatment group, and as we can see, the age and the age range are fairly comparable throughout.

All of the demographics are roughly comparable for the four treatment groups. Two-thirds of the patients are females, nine-tenths are white, two-thirds are between 35 and 64 years old.

We might note, there were 127 patients over age 65 at this time, who were in the nefazodone group.

This slide shows the number of all patients receiving nefazodone, according to overall modal dose and duration of therapy in Phase II, III studies.

To explain this slide, we look at this cell right here. There were 588 patients who took nefazodone between 32 and 90 days, and the modal dose was in the 200 to 399 milligram per day range.

Eighty percent of all patients had a modal dose between 200 to 600 milligrams per day. Only 14 percent of the patients were treated longer than 181 days.

This slide shows the patient exposure in the Phase II, III depression trials expressed in patient exposure years. To illustrate, one patient taking nefazodone for 12 months counts as one patient exposure a year.

Likewise, two patients taking nefazodone for six months, or four patients taking nefazodone for three would all count as one patient exposure year.

We see the patient exposure years in this column, and I would like to point out the relative exposure rations, particularly nefazodone to placebo, which we may want to keep in mind in slides coming up.

Our safety review consisted of describing the common event profile, through ADR tables, labs data, vital signs and ECG data.

Additionally, we looked for serious and uncommon events, such as deaths, patients who dropped out due to adverse events. We performed special searches, such as a suicidality search, which will be described in a moment.

We also searched for potentially important changes in labs, vital signs and ECGs.

Several short term placebo controlled trials of a similar design were combined to obtain the following list of common nefazodone related adverse events.

These events occurred in more than five percent of nefazodone patients and were significantly higher than in the placebo group.

Our events are dry mount, somnolence, dizziness, light-headedness, nausea, constipation, asthenia, and blurred vision. These same events will continue to come up in the next few slides.

We also looked for adverse events for which dose dependency was observed in dose comparison trials. This data comes from trials 004A and 004B. There are doses where up to 300 milligrams for the low dose, up to 600 milligrams for the high dose.

A Fisher's Exact Test was used, and

these events occurred more frequently in the high dose group -- nausea, dizziness, somnolence, abnormal vision, constipation and confusion.

Other variables evaluated included serum chemistry, hematology, urinalysis, vital signs, and ECGs.

In our search for the serum chemistry variable changes, we had two methods. One was a comparison of groups unchanged from baseline, and then a comparison of groups on incidence of drop out.

The methodology for the comparison of groups on change from baseline was to compare treatment groups, or four different groups, for a pool of short-term trials, and the incidence of patients with potentially clinically important change in serum chemistry variables.

There were no statistically significant nefazodone placebo differences.

When we compared treatment groups for a pool of all Phase II, III studies on the incidence of patients discontinuing for changes in serum chemistry variables, the results are as listed here -- 14 nefazodone patients discontinued, 5 active control, and 2 placebo patients. The

corresponding percentages are listed in this column.

Most of the discontinuations were for increased serum transanimase. These included 12 of the 14 nefazodone patients and all of the active control and placebo patients. For nefazodone, none of the patients had jaundice, for whom any follow up data is available. Two of these patients had malaise and the rest were not symptomatic.

All of these patients had favorable resolutions upon cessation of medication.

We also looked at hematology variables. And our comparison of groups on change from baseline did show that nefazodone, at a P of less than .01, had lower hematocrits, as compared to placebo.

We defined lower hematocrit as less than 32 percent in females, less than 37 percent in males.

Additionally, we looked at mean laboratory data across treatment group. This tended to confirm the finding with the nefazodone group having a decrease of 1.5 to 2 percent in their hematocrit, and there was some suggestion of dose dependency.

We also looked at comparison of groups on incidence of drop out. Eight nefazodone patients

dropped out and one placebo patient and these are the corresponding percentages.

It is somewhat reassuring that only two of these eight drop-outs resulted from anemia. One was a pre-existing case and the other had a GI bleed.

There were also four lipopenia cases, all with normal differentials. One of the four had clinical symptoms. Another patient had a pre-existing thrombocytopenia and another patient had mononucleosis.

I might mention, again back up here, of the patients who were identified as having a low hematocrit, there were 24, and only 2 of the 24 was symptomatic. The one would have an acute GI bleed, which resulted in a hematocrit of 26, and that patient dropped out. And then, another patient had a GI bleed, but continued in the trial.

We looked at urinalysis variables in our comparison of groups on change from baseline, identified no statistically significant nefazodone placebo differences.

The comparison of groups on incidence of drop out showed only one nefazodone patient and one active control dropping out. The nefazodone patient

had hematuria and was later found to have a bladder carbuncle.

Looking at the vital sign and weight changes, we did identify a statistically significant different at the P less than .05 level, with nefazodone patients having a tendency for low systolic blood pressure.

This was defined in our criteria as blood pressure less than 90, with a decrease of 20 millimeters of mercury from baseline.

Fifty-three patients were identified as having lowered systolic blood pressure. Thirteen were symptomatic, complaining of either light-headedness of dizzy, but there were no cases of syncope.

Four of these patients were identified as having postural hypertension and will be discussed in a moment. One of the patients was identified as having sinus bradycardia, and that will be discussed in a moment also.

The comparison to groups on incidence of drop out showed nine nefazodone, nine active control, and three placebo patients dropping out with the corresponding percentages.

Of our nine nefazodone drop outs, three

patients dropped out with hypertension. In two, it was per-existing. One patient dropped with tachycardia and was thought to have had a panic attack.

One had elevated temperature with mononucleosis. Two discontinued due to weight gain, and two discontinued due to weight loss.

Our general conclusion is that there is a nefazodone effect on blood pressure and, in a moment, I will get to the slide on orthostatic hypertension and describe that in more detail.

We compared the groups unchanged from baseline looking at ECG data, and identified, at the P .05 level, that sinus bradycardia was more common in nefazodone than placebo patients.

This was defined as having a heart rate less than 50 beats per minutes, with a decrease of 15 beats per minute from baseline.

We also looked at mean laboratory data across treatment groups, and this confirmed that the nefazodone group tended to have a decreased heart rate of one to four beats per minute. And this was confirmed by the pulse rate also.

And once again, there was a suggestion of dose dependency, seeing the trend somewhat larger

in the high dose group than in the low dose group.

Of ten patients that had sinus bradycardia, three were symptomatic. One of these three also was in our low systolic blood pressure group.

Of the seven patients who were not symptomatic, one later dropped out because of an AV block.

Comparing the groups on incidence of drop out, we find 13 nefazodone drop outs, four active control, nine placebo, and corresponding percentages.

Four patients dropped because of PVCs, one with extra-systoles, one with atrial fibrillation, one with sinus bradycardia. There was one with a third degree AV block, one first degree AV block, and four blocked with STT wave changes.

This slide shows crude and adjusted mortality rates for Phase II, III depression studies. The crude rate is given here. There were five mortalities in nefazodone, one in tricyclic, with the corresponding percentages.

Adjusted for exposure time, the rates are given here, per 100 patient exposure years.

We looked for serious adverse events

through an expanded data base that had a cut off of April 15th of 1993. At that time, there were a total of 9 nefazodone deaths, all suicides. Nefazodone did not play a role in any of these suicides.

This slide shows suicide and suicide attempts in patient exposure years through this expanded nefazodone safety data base of April 15th of 1993.

By this time, the N for nefazodone is much larger, patient exposure years have gone up correspondingly.

All of the suicides found were in the nefazodone groups. The suicide attempts were spread across all treatment groups, with the rates per patient exposure year in this last column.

This slide shows the rates of drop out by treatment group and reason, for the pooled Phase II, III data base. The treatment groups are listed here with the Ns below.

As might be expected, placebo had the highest drop-out rate due to lack of efficacy. Placebo also had a very low rate due to adverse experiences. Nefazodone was somewhere in between the placebo rate and the tricyclic rate. Total drop

outs are as shown here.

This slide shows the common and drug related adverse events showing drop outs in nefazodone treated patients. These were defined as events occurring in more than one percent of the treatment group, with the nefazodone group having an incidence of twice the placebo group.

Once again, we see many of these same events -- nausea, dizziness, insomnia, somnolence, asthenia.

This slide shows the occurrence of common adverse experience over time, the cohorts of nefazodone treated patients with onset of the experience during week one, and who completed treatment into week six, in short term placebo controlled trials.

To explain this slide, let me stress that these are patients who completed treatment. Any patient who dropped out along these six weeks is not represented in this slide.

Every patient who complained of one of our common adverse experiences in week one is listed in this column. Each week thereafter we see the percent of those same patients who still are complaining of the adverse experience in the first

column.

Please note that by week six, the percent of patients has dropped considerably in all categories, with only 17 percent still complaining of light headedness and up to 60 percent still complaining of dry mouth.

We specifically looked for a couple of adverse events which we thought were likely to be drug related. We looked for mania, hypomania, and for syncope postural hypertension.

This slide shows the occurrence of mania, hypomania, in clinical trials. In the monopolar patients, the occurrence rate in nefazodone is about what it is in tricyclics. In the bipolar group, nefazodone had a rate of 3.2 percent. The occurrence rate in the tricyclic group was 10 percent.

We also looked for the occurrence of syncope postural hypertension in Phase II, III trials. As you can see, for syncope, nefazodone and placebo rates are about equal, somewhat less than what is seen in tricyclic.

For postural hypertension, the nefazodone group is somewhat above the placebo rate and the SSRI rate, but certainly it is less than the

rate seen in the tricyclic group.

This, in general, supports out finding from the mean laboratory changes that were shown in a previous slide and confirms, probably, the weak alpha adrenergic blocking activity of nefazodone.

A number of formal interaction studies were done. Haloperidol shows decreased clearance, with the AUC being 1.36 times higher.

Triazolam shows decreased clearance, with the AUC being four-fold higher. Alprazolam shows decreased clearance with the AUC being two-fold higher. Lorazepam and Cimetedine shows no PK interaction found.

There is limited experience with nefazodone overdose in humans. There were only two overdoses in clinical trials. One patient took 3400 milligrams, the other 3600. Both fully recovered. Vomiting occurred in one patient.

Neither patient had alterations in vital signs, ECGs or laboratory tests.

My conclusion regarding safety was that a review of the clinical trials database for nefazodone of over 2680 patient exposures revealed no adverse findings that would preclude its use as an antidepressant.

That concludes my slide presentation. Are there any questions.

DR. TAMMINGA: Thank you, very much, Dr. Hearst.

DR. HAMER: I assume that the comparison to SSRIs were in the Phase II trials.

DR. HEARST: Yes.

DR. HAMER: Do you know, were there many SSRIs or was there one in particular. Were they different drugs or the same drug.

DR. HEARST: I guess it was fluoxitine throughout.

DR. FRANK: What proportion of the patients included in these trials were bipolar, and how is bipolar defined.

DR. HEARST: Off hand, I am not sure that I have that readily available. Perhaps the sponsor could reply to that.

DR. ROBINSON: It was a relatively small number.

DR. FRANK: Did that include bipolar I and bipolar II patients or just bipolar II patients.

DR. ROBINSON: I am not certain if I have that information.

DR. HEZEL: I have two questions. ECGs

and suicide, were the bradycardia in elderly only or all age groups.

DR. HEARST: I believe they were throughout all age groups. I don't know the exact break down by age, but they weren't exclusively in the elderly.

DR. HEZEL: And could you revisit the suicides and talk about how you conclude there is no relationship there, in regard to the drug. You have nine successful and twelve attempted.

DR. HEARST: You mean, as compared to other treatment groups. Well, in that slide, if you look at -- maybe we should put that slide back up. You know, it would seem that only one or two suicides in other groups would bring the percentages back to equivalent to nefazodone.

I can't tell you why all nine suicides were in nefazodone, but I think statistically we are just within an occasional event in one of the other groups, which we didn't have. The other groups, of course, have a zero rate.

DR. TAMMINGA: It is a large data set of 2600 patients, so that there are too few events to make a firm connection.

DR. LAUGHREN: If I can just comment

here, it is not a surprising number of suicides, having looked at a lot of antidepressant databases over the years. This is not an unusual number.

I think if you have that slide in front of you, it is -- I guess we are not going to be able to bring it up. If you look at the relative exposure time for the different groups in that comparison, it is roughly five-to-one, nefazodone to placebo.

It is roughly six-to-one for nefazodone to the tricyclics. So, if you had one or two events in the other groups, that would completely wash away the findings.

We don't have statistics on these comparisons, but the confidence intervals are going to be fairly wide. It is not an unusual finding.

DR. CASPER: I agree with Dr. Laughren, this is not an unusual finding, the number is very small. On the other hand, if you would perhaps examine whether these patients were suicidal to begin with, because if you look at the total Hamilton score, these patients were moderately depressed, on average. So, you wouldn't necessarily expect a high suicidality.

And if these patients, for instance --

what we might want to look at is where did these patients rate on the Hamilton depressions scale, and whether these were de novo events, or whether they rated, to begin with, on the scale.

DR. LAUGHREN: There is an additional analysis that may shed some light on this that we didn't have access to as part of the NDA. If I could address this to the sponsor, I understand that you may have done an analysis looking at emergence of suicidality. Did you do that. We didn't have that as part of the package that we reviewed, I don't believe. But maybe, in your presentation, you can present those findings. That sort of gets at the question that you are asking.

But the other problem here -- there is one other problem. Doing an adjustment for time, simply looking at patient exposure years, doesn't address the possibility that there is a change in the hazard rate over time.

Again, it is somewhat unfair to nefazodone here. You have much longer exposure -- many patients exposure much longer than the short-term phase of the study, during which monitoring isn't as good. The probability of the event may change during that period of time and make it very

difficult to make these kinds of comparisons.

DR. CHARNEY: My question was relative to that point, which is when, in the point of treatment, did these suicides occur, because if that data was available, it would be helpful. If it all occurred in the first two or three months of treatment, that would be different than if they occurred scattered throughout the treatment periods.

DR. TAMMINGA: Perhaps the company could incorporate that into their presentation.

DR. LAUGHREN: I think we have that data here.

DR. HEARST: That data is available. I don't have it with me right now. Some of the suicides were fairly far out, some occurred shortly after the short term trials were over.

DR. LAUGHREN: I can try and summarize it here. We have data on the duration of treatment at the time of the suicide for the nine patients. And it ranges from 17 days at the earliest to 366 days. And it tends to be fairly spread out.

I mean, there are a number that occur early, many others that occur late. I will just pass it down to you so that you can get a look at it. But it doesn't suggest any clustering at one

particular time point.

DR. HEZEL: Would you repeat for me what you said about bioavailability with food, and whether or not you think the 20 percent decrease has any impact.

DR. HEARST: I think the clinical effect isn't known. There is an absorption delay also, but I don't know what to make of it. Perhaps the sponsor has some recommendations.

DR. LAUGHREN: One other comment on that question. This food effect study, I believe, was a single dose study, and maybe, Ray, you could address that. It is often hard for a drug that is going to be used chronically, what a finding like this from a single dose study, would have during chronic use.

It may actually diminish even this effect during chronic dosing. The increment would be less.

DR. LIN: I have several technical questions. The first question is about availability. You mentioned that it is 15 to 23 percent. That seems to be fairly low. So, I wonder what is the reason.

And the second question is about a non-linearity of the pharmacokinetics. What do you

think is the reason for that and what is the possible clinical significance of that.

And the third question is about the blurred vision, constipation and confusion. Does this mean that this drug may have anticholinergic effect.

I think in the description earlier it says that the drug doesn't have anticholinergic or histamine effect.

The last question is about the gender/age interactions. I wonder if you could comment on that.

DR. HEARST: You know, one thought about the gender and age interactions is that the elderly females have higher levels. And one thought was, perhaps it had something to do with their body weight. But I don't know at this point whether that is the only reason. That is a possibility.

The drug is not thought to have any anticholinergic activity. I have forgotten your other question.

DR. LIN: What is your explanation about the high incidence of the vision problem and constipation and confusion.

DR. HEARST: I don't have an

explanation.

DR. TAMMINGA: Perhaps the company, in their presentation, could concentrate on whatever explanation for that is available.

DR. HEARST: I think you asked about the nonlinearity also. And one speculation is that metabolic pathways become saturated. And that may contribute to it.

DR. LAUGHREN: Also, you had a question about the low bioavailability. This drug is extensively metabolized. There is a lot of presystemic clearance.

This is not an unusual absolute bioavailability. It turns out that it is fairly infrequent that we get these kind of data for psychotropics. You don't often see the numbers.

But in fact, many drugs are extensively clear presystemically, and then, if you had absolute bioavailability data, you would see the same kinds of figures.

So, most of it is first positive effect. Ray, maybe you could respond to that. I assume that it is first pass. Is that your impression.

DR. TAMMINGA: You may want to come up to a microphone and make a comment, if you wish,

since I think that a lot of the committee members have these kind of questions.

MR. BAWEJA: Ray Baweja, division of biopharm, FDA. In response to his questions, I have the following to add.

Essentially, yes, the drug does display a non-linear pharmacokinetics, both for the parent compound and for the hydroxy metabolite, which is considered to be equally active.

We have seen -- Dr. Mele's presentation talked about low dose and high dose. In terms of non-linearity, we have seen doses up to 200 milligrams BID which just takes it up to 400 milligrams daily dose. So, we are looking at a non-linear drug.

I see numbers here, four times greater than expected for AUC and C Max. So, we only know non-linearity characterized up to the 400 milligram daily dose. We don't have it characterized all the way up to the 600 milligram dose.

In response to your question about absolute bio, it is low. It is extensively metabolized to several metabolites and that number, therefore, appears low. You had another question, I believe.

DR. LIN: The other questions, one is about the possibility of anticholinergic effect. The other one is about gender/age interactions.

MR. BAWEJA: Yes, again, in gender and age, we can just take it all along the side of elderly females, showing higher numbers than young females. And if it were on genders, elderly females are, again, higher than elderly males. That is about the best we could tease out, if the sponsor would like to add any more to that.

DR. LAUGHREN: Ray, was an attempt made to adjust for weight.

MR. BAWEJA: I think the explanation was thought of along those lines but I don't think we were that far yet, or have done it, so far.

DR. TAMMINGA: Since the hydroxy metabolite is equally active with the parent compound, if you were to add those together, what would be the apparent bioavailability then.

MR. BAWEJA: Yes, I think if I were to answer you and give you a total comprehensive picture, let's assume the parent is one unit of activity.

The hydroxy metabolite which closely tracks the parent is another full unit of activity.

The NCPP is a minor metabolite of sorts, when we look at the quotient of exposure and activity.

And the third one, the dione, may be present four times more, but is one-sixth less. Therefore, we come to a number something like a quotient of two-thirds. So, we have one plus one plus a two-third. That is the full slate of events here.

And then again, like I said, non-linearity is seen for the parent and the hydroxy. It has gone up to 4X for parent. And I think that is how high it goes for the -- maybe a little less for the hydroxy.

The down numbers for linear/non-linear aspects come out a little less.

DR. LIN: A follow up to the question of the non-linearity of kinetics. If the explanation is that it is because of a situation of an enzyme, do we know which enzyme that is, because the question here would be that if one enzyme is saturated, it may have a significant effect on other drugs which are also metabolized by that enzyme.

DR. BAWEJA: We haven't seen an isozyme characterization per se. We surmised that the minor metabolite NCCP, when it degrades further, is

probably is about a 36, but do we have a characterization of isozymes along these lines.

DR. ROBINSON: We have not done any direct studies with isozymes. The drug interaction studies, mentioned by Dr. Hearst, would suggest that isozyme does have an effect on the drop in the enzyme system. Direct studies have not been done.

DR. LAUGHREN: I think that is a particularly important question, though, because I believe that triazolam is probably metabolized by P450 3A4, an enzyme which has been implicated in several other important interactions.

If that enzyme is being inhibited by nefazodone, it could be a marker for other potentially important interactions, for drugs that are likely to be used with nefazodone. So, it is a particularly important point to follow up on.

DR. TAMMINGA: If there aren't any more questions from the committee, thank you, Dr. Hearst. And we could ask you, Dr. Laughren, if that concludes the FDA presentations.

DR. LAUGHREN: That does, that is correct.

DR. TAMMINGA: In that case, we will take a 15 minute coffee break and we will take it --

it will truly be 15 minutes. So, everybody, would you please come back on time.

(Brief recess.)

DR. TAMMINGA: We will continue with our nefazodone discussions and presentations and Dr. Donald Robinson from Bristol-Meyers will present for the company and answer our questions.

Agenda Item: Sponsor Presentation, Bristol-Meyer Squibb.

DR. ROBINSON: Thank you, Dr. Tamminga, and Dr. Leber, Dr. Laughren, other members of the division, and members of the committee.

A number of interesting questions were raised during the discussion by the committee and I will try to address those as best I can.

One question regarded the proportion of patients who were responders, who were rated as responders to drug treatment.

And of course, that really has to be looked at in the context of in comparison to non-drug treatment of placebo. And I think a table that would perhaps summarize this briefly is C-51.

This is a table which has other information on it. But what I would like to point out is that the clinical, global improvement rating

of much improved or very much improved at end of treatment was one of the two primary outcome measures that we employed in all of the efficacy trials.

And this summarizes some results and the results across trials at measure.

The analysis is showing -- the first week at which drug/placebo difference was evidenced is shown on these studies, which Ms. Mele has spoken to in great detail. And within the fixed dose study, we show it by fixed dose treatment arm.

And I think it is apparent -- now many of these studies were six week trials and only two were eight week trials.

The percent responders were in the range, for the treatment group mean, of 55 to 65 percent in studies. So, that is sort of a general overview of what we observed across the phase II and phase III studies.

DR. HEZEL: Do you have numbers of patients. That is what I was looking for, not the percent, numbers versus percent. Out of your population of 2,000, what were the number of responders.

DR. ROBINSON: The placebo controlled

trials encompassed about 1,000 patients across the A trials, who were randomized to nefazodone.

As you know, some of the treatment arms randomized to restricted dose range and others to the full dose range.

In the full dose range, there were approximately -- I don't have the exact number in front of me -- approximately 300 to 400 patients on nefazodone who had the opportunity to receive nefazodone within its full dose range.

As I said, in that group, on average, we were seeing percent responders ranging somewhere from the low 50s to the 60s, percent of patients.

I would like to next make some comments about the dosing of nefazodone. The problem of how to dose and define the therapeutic range of a psychopharmacologic agent is a difficult issue, as most of you know.

And there has been, always, some difficulty in establishing the dose range early in the development program for new antidepressants.

One way to look at the appropriate dose range is to look at the dosing experience in the placebo controlled trials, where the patients had the opportunity to be dosed within the full range.

So, this shows an analysis of the -- it is a meta analysis or a grouped analysis, I should say, of the patients who were randomized across studies to the dosage arm that allowed dosing up to 600, except in the case of 003, in which the maximum dose is 500 milligrams a day.

So, if you plot the end of treatment dose, the dose to which patients were titrated at the time they completed treatment or discontinued from the study, across the X axis, starting from 100 up to 600, we show the Ns down here in each arm.

And you plot that against those patients rated as responders on the CGI improvement scale -- that is, the percent much improved or very much improved on the Y axis, the distribution for end of treatment dose in these studies was as shown here.

And the percent responders was highest in those who had an end of treatment dose of 300 milligrams a day, and a rather similar, slightly lower response, in those patients whose end of treatment dose was 400 milligrams a day and 500 milligrams a day.

However, it is obvious that some patients, in fact, were responding at lower and higher doses, but that is presumably a minority of

the patients.

DR. LAUGHREN: Don, if I could just make one comment, since you have the slide up here, and repeat a caution that Bob Temple raised earlier, these are all titration studies.

And if you have a subgroup of non-responders in the population, they are the ones who are likely to be pushed to the highest doses. So, I am not sure that you can conclude from this, necessarily, that that dose range of 300 to 500 is the best dose, unless you have looked at it in the proper way.

DR. ROBINSON: I think that it is the dose range that we studied. I would agree with you that it is very difficult to interpret the response rates at the two extremes of the curve, because patients tend to get pushed to high doses if they have not responded at lower doses, and they obviously tend to stay at lower doses if adverse experiences seem to be dose limiting.

So, I would not claim that this is a dose response relationship. I would merely say that it is the experience in dosing across all studies, where the patients had the opportunity to be dosed within that range.

Would you like to discuss any other aspects of the dosing.

DR. CASPER: Another consideration, Don, would be to look at, since patients also obviously dropped out for lack of efficacy or non-responder status, what you are showing us is really the last observation carried forward.

DR. ROBINSON: That is correct, that is an LOCF analysis.

DR. CASPER: So, this is a select group on top of the flexible dosing.

DR. ROBINSON: Well, it is an intent-to-treat sample and LOCF. So, all patients are counted.

DR. CASPER: So, this is an intent-to-treat sample.

DR. ROBINSON: It is an intent-to-treat sample, so it is all patients.

DR. CASPER: But this end point dose is at what time, though.

DR. ROBINSON: It is their daily dose during their last week of treatment, whether they were completers, or they might have discontinued earlier.

DR. CASPER: So, this one includes the

ones that have discontinued.

DR. ROBINSON: Yes.

DR. CASPER: So, really, it is a very mixed group.

DR. ROBINSON: Well, it is the total sample that had the opportunity to be dosed within the full range that we studied, 100 to 600 milligrams.

DR. CASPER: And they might also, the ones who have reached, at some point, 600 milligrams, might have been dosed by week six or seven or week four or five, again down to 400 or 500.

DR. ROBINSON: That is correct. And you might have seen some evidence for that when the grouped data, dosing data, was shown by Ms. Mele, in some studies.

I think some point of confusion that has arisen from the fixed dose trial, which is one of the early studies we conducted in phase II, and not to get into, I think, a fairly complicated interpretation, I think one of the things that wasn't brought out, but I think it might be helpful to you, is to understand that those patients assigned to all of the doses -- 50, 100, 200, 300 --

were not initially titrated to those doses. They started at those doses.

One of the things we learned from that study, we believe, and I think that the data support it because of the drop out patterns, was that patients starting at 300 milligrams a day did not tolerate the drug as well.

And therefore, it affects the end point analysis and the LOCF analysis, because you have a differential drop out rate in the high dose group.

We are sensitive to the value in doing fixed dose trials, although they have limitations as well, and it probably would be preferable to have given a titration in all arms of that study, within a reasonable period of time, up to their fixed dose.

DR. LEBER: Don, what years was the fixed dose conducted over, I mean, secular time.

DR. ROBINSON: Approximately 1985 to 1987.

DR. LEBER: The reason I raise the point, always, is that there is a retrospective criticism that arises because you are operating with your overview of 1983, applying it to design features from 1985. And the points that are now well understood by most may not have been understood

in 1985.

DR. ROBINSON: There was a question about the emergency of suicidality raised by Dr. Casper. We will display that analysis.

In this analysis, we are looking at, again, the placebo controlled trials. I would point out that, in the placebo controlled trials, as is customary, an exclusion factor was to enter patients who had significant suicidal ideation.

So, there were not very many patients who had extreme values on the suicide item on entry. But it does allow one to then do an analysis for patients who, on Hamilton item 3, starting with a zero or one, at some point during treatment, reached a maximum value of three or four.

And these are the results for nefazodone maximum and end of treatment. These are the numbers of patients who, at some point in time, achieved a score on item three of three or four, with nefazodone, with placebo, and with tricyclic. And these are the end of treatment data by the same approach.

There was a question about some of the side effects of nefazodone. I think it is probably helpful here to look at the placebo controlled data

for the common adverse experiences, that, that is, that differed significantly from placebo.

The question was posed about the incidence of somnolence, constipation, and blurred vision. Again, I think that it is helpful to compare the adverse experience incidents to the other control groups.

And you can see that for dry mouth, it is somewhat greater, of course, than placebo. Obviously, as one would expect, much less than for the tricyclic.

The pharmacology of nefazodone indicates that it does not bind to the cholinergic receptor and there is no evidence of cholinergic effects.

The explanation, then, for this modest increase in dry mouth is a little bit uncertain, but many would argue that it may be the alpha adrenergic blocking effects which nefazodone does effect, although you could not rule out a serotonergic effect, since there is some evidence that this may also be reported with serotonergic drugs.

Similarly, for somnolence, you see the pattern that there is an increase when compared to placebo, although less than was reported for the tricyclic.

Again, this is a modest difference and the explanation, again, I think, is difficult from the pharmacology.

My interpretation is that it is also reported with other serotonin reuptake inhibitors as a significant adverse experience.

And I would think the blurred vision, 6 percent for nefazodone versus 3 for placebo and 8 for tricyclic, again, most likely reflects the alpha adrenergic effects.

You also raised the question about whether we looked at the side effects by gender and by age. And I think it would be helpful if we could look at the breakdown of these side effects by gender.

Stratifying on these common adverse experiences by sex, we found that these are the common AEs that we have been talking about. We found that only lightheadness is more common in men in the nefazodone groups. The other seven did not differ.

With regard to age, it might be helpful to look at the incidence of serious adverse events across the entire database of approximately 2200 patients, of whom 127 in this analysis were elderly.

And these are serious adverse events by the regulatory definition and we saw no evidence of a greater liability in the elderly compared to the younger. There was a 3 percent, approximately, incidence in both groups.

DR. SCHOOLER: Could I just ask one question about that. Would the length of exposure have been about the same for the patients under 65 and those over 65.

DR. ROBINSON: I think if anything, on average, the length of exposure was greater in the elderly because they tended to be more highly represented in the open trials, which had the purpose of seeing long term experience.

DR. TAMMINGA: Don, a lot of the side effects that are most bothersome in the elderly, of course, are not the serious adverse events. Do you have any idea for the more common things like constipation and somnolence, what this comparison would look like.

DR. ROBINSON: Yes, I think that I can show you the common adverse experience broken out by age as well. This compares in the younger and in the elderly for the eight common adverse experiences. The incidence with nefazodone in the

two groups.

Now, because this is the placebo controlled data base, these are relatively small numbers, of course, for elderly.

Elderly were not excluded from the placebo controlled trials, so we do have a small number. And in general, there did not seem to be important differences in the incidence for the elderly versus the younger, with the possible exception of asthenia.

DR. HAMER: A change in one patient there would have been like five percent or something difference. I mean, those aren't very stable estimates in the groups with low ends.

DR. LEBER: I have a methodological qualification I think may be important. I assume these are spontaneously reported.

DR. ROBINSON: That is correct.

DR. LEBER: They are not cued or checklist solicited.

DR. ROBINSON: That is correct. These are spontaneously reported.

DR. LEBER: And therefore, is there not likely to be tremendous variation between centers and investigators in what is declared an event and

collected as one. And there is no attempt to make these comparisons within single studies, but these are aggregated data.

DR. ROBINSON: That is correct.

DR. LEBER: The reason I raise that, obviously, is the hazard of comparing, you know, marginals where individual cells may be the important locus of the comparison.

And these rates, to compare to studies that used a systematic method of inquiry to produce these ADRs would also be difficult to compare with because of the obvious methodological problem. I think that is an important groundwork for discussing these numbers.

DR. ROBINSON: We would agree there are limitations to the interpretation of the data.

Finally, there is a question about the number of bipolar patients in the sample. There were 64 bipolar patients out of the 2200, approximately, nefazodone treated patients, for a rate of about 3 percent.

They were all enrolled when they were bipolar depressed, of course.

DR. FRANK: Could you comment on whether they were bipolar I or bipolar II. I think that is

really important.

DR. ROBINSON: Well, it could be important but I am unable to answer it today.

If there are no other specific items to be addressed, I would like to end with just a few comments about the drug.

I want to thank the agency for an extremely thorough review of the NDA and express a general agreement with their conclusions.

Obviously, the comprehensive nature of the preceding reviews with Dr. Hearst and Ms. Mele makes little need for extensive comments at this time. But I would like to emphasize a few points for further clarification.

I plan to briefly highlight nefazodone's pharmacology, some findings of particular interest during this clinical investigation, and to give some recommendations about clinical use.

Briefly, the methods of action to be a dual mechanism by blocking -- it is a potent blocker of 5 HT2 receptor sites. It is also a serotonin reuptake inhibitor.

And pharmacologic studies show that it significantly down regulates cortical 5 HT2 receptors, but not beta receptors.

Several well controlled trials showed nefazodone is an effective antidepressant, in studies enrolling patients with major depression.

Nefazodone's efficacy generally appears to be similar to Imipramine's in the controlled trials. Some additional meta analyses of data from the eight placebo controlled trials were conducted and also showed that nefazodone is effective in subpopulations of interest, for example, those patients who are more severely ill, defined by a CGI rating of markedly ill, and those patients who have prominent anxiety symptoms associated with their symptoms, based on a pretreatment Hamilton anxiety scale score of 19 or higher.

So, nefazodone appears to be effective across a broad range of patients meeting criteria for major depression.

Dr. Hearst has addressed many of the points in the search of the nefazodone safety base. No evidence was found of untoward effects that have associated with some other antidepressant drugs or with the antidepressant drug class in general -- that is, so-called class safety issues.

There was no difficulty experienced in the small number of patients that took rather large

doses of nefazodone in the suicide attempt. And the patients had mild to transient symptoms and rapidly recovered.

Weight and appetite were not adversely affected during long-term treatment and there was little, if any, sexual dysfunction, and no treatment emergent anxiety symptoms associated with nefazodone therapy in these controlled trials.

This would suggest that, in clinical use, nefazodone treated patients would not experience some of the particularly troubling side effects of some of the other agents.

We have already spoken to some of the common adverse experiences in some of the controlled trials. What I have listed here are those that meet the criteria for common adverse experience for either active drug. So, this is the total list for Imipramine and/or nefazodone.

It is of some interest, that in general the interest with nefazodone there were not only fewer common AEs, but except for nausea and lightheadness where there were slightly higher incidence on nefazodone compared to Imipramine, in all others, it appeared to be lower.

Another index of a drug's safety and

tolerability is the rate of premature discontinuation from treatment for reason of adverse experience.

This is the total experience with nefazodone, both acute, long-term controlled and placebo controlled and open studies. And nefazodone's rate of 15 percent discontinuation for reason of adverse experience compares favorably to placebo, which is 10 percent, and tricyclic which, overall, is 20 percent.

The findings from the extensive studies of differing designs during the phase II and phase III development support nefazodone's recommended use with the following guidance about dosing, in our opinions.

It is effective with BID administration. The initial dose should usually be 200 milligrams a day for most patients. Dose increases are indicated for most patients based on clinical response following a week of therapy.

Let me make one final point. In the efficacy studies, as I had indicated in our previous discussions, there was a pattern that most responders in the titration studies were receiving an end point dose of 300 and 500 milligrams a day.

So, in summary, serzone, the trademark for nefazodone, represents a novel antidepressant drug, in our opinion, because of its dual effects on the serotonin system.

Its efficacy and advantageous safety profile have been established in a comprehensive program of studies designed to carefully define its therapeutic use.

I thank you very much, that is the end of my formal comments. And I and other colleagues involved in the investigation of nefazodone are available for further questions.

DR. TAMMINGA: Thank you for your presentation, Dr. Robinson.

DR. HAMER: On about your fourth slide, the one entitled efficacy summary, your third bullet is, effective in markedly and moderately ill patients with major depression.

Could you perhaps expand a little bit on sort of what that statement is based on. Was it compared with a comparison to placebo in people at that level of depression, or was it based simply upon some sort of change from baseline.

DR. ROBINSON: That is based on a meta analysis of all eight placebo controlled trials,

comparing the outcome, the primary outcome measures, in patients who were randomized to the treatment groups allowing the full dosing range and compared to placebo.

DR. HAMER: So, it is compared to placebo.

DR. ROBINSON: It is compared to placebo, right. And it is highly significant, as one might expect, when you have large numbers.

DR. CHARNEY: There were some center differences in the data and in your looking at it, analyzing that data, is it relevant to specific patient subtypes in terms of response. In general, what did your analysis reveal in terms of center differences.

DR. ROBINSON: My general answer is it is difficult to explain differences in outcomes of studies, and one can only speculate retrospectively why you observe different results between studies and between centers within the same study.

It is our opinion that the differences in 006, as Ms. Mele pointed out, had a lot to do with the implementation of the study, with its exceedingly high drop out rate, for all treatment groups. It was much higher than one would normally

expect.

So, it is both very difficult to see a rationale for combining those findings with the other site in that study, which had a fairly reasonable implementation strategy and a reasonable retention rate of patients.

In the other study where the question was raised about the possibility about site differences, I think again it is speculation, primarily, but there was a higher placebo response rate in those psychiatric treatment facilities as compared to the other sites.

But actually, the degree of change on all treatment was of the same -- I am sorry, the degree of change or improvement on the two active treatments was approximately the same as in the other site. Again, it is difficult to know, in retrospect, exactly what the explanation might be for that.

DR. SCHOOLER: I would like to get back to the slide that you showed on common adverse experiences.

One of the issues with the nefazodone group, if I understand it correctly, is that that would include the low dose nefazodone cases, which

is a dose lower than one would anticipate using.

Do you have that broken out, at some point, by dose, so that one could compare what we would consider the effect of the nefazodone group to the Imipramine which were clearly in the effective range.

DR. ROBINSON: Yes, the question was the nefazodone data includes patients who were dosed within a restricted range and a full range; that is correct. It obviously would be somewhat different if you broke it out according to dose range.

I do not have the data that I can give you to show you, but I can tell you that it is somewhat higher, as one would expect, in the patients who had the opportunity to be dosed in the full range.

But there was nothing in there that would suggest safety concerns to us, because patients should be dosed and titrated according to their clinical response.

DR. HEZEL: I am sorry, I am back on the numbers question again. As close as I can figure out, about 353 subjects were in the therapeutic range that you are basing positive effect on. Am I close.

DR. ROBINSON: In that analysis, that is correct.

DR. CASPER: I have two questions, one about efficacy and the other about headaches, an adverse effect we really haven't discussed much, because I think the incidence was not much different from the placebo responders.

Maybe since that is a quick question, because in research trials, NCCP, one of the metabolites, I think, has produced migraine headaches, or migraine-like headaches, I was wondering whether the quality of the headaches in nefazodone treated patients was different.

From the data we could just see the headaches. Maybe you want to answer that.

DR. ROBINSON: I think that is a good question and I agree that there could be a qualitative difference in headache, possibly due to NCCP if it is present in high concentrations.

To the best of our knowledge in looking at it, because we were interested in that question as well, we could not ascertain any qualitative differences.

And the overall incidence of headache, as you pointed out, was the same across the

treatment groups. So, overall, there is no increase in incidence.

The other point about NCPP that might be of interest to you is that the effects of nefazodone and hydroxynefazodone are in opposition to those of NCCP on the 5 HT1C2 receptor. And this might suggest that you wouldn't see those troubling side effects with NCCP.

DR. CASPER: Thank you. The other question related more to efficacy, because you said you did agree with Ms. Mele's interpretation of the data.

You showed us, in the efficacy data, only the global improvement data; correct.

DR. ROBINSON: Correct.

DR. CASPER: Whereas, we saw data which indicated a depressed mood really did not show that much of an effect, although if you take all the symptoms together -- somatic, anxiety and guilt and so on -- you do see an effect.

DR. ROBINSON: Well, my interpretation of that is that there was a lot of heterogeneity, I thought, in the drug effect on those measures that Ms. Mele showed. Across studies, there was a lot of heterogeneity.

I can't explain that. It could be the samples were different or the rating was different. In some of the studies, as Ms. Mele summarized for you, there was significant improvement on the depressed mood item one, and overall, I thought that when you look at the four or five measures of efficacy measures, that there was a pattern of superiority of nefazodone to placebo.

And I guess my final comment would be that the studies are designed and powered but the statistical power analysis is to detect difference on generally one or two outcome measures.

And the ones we chose were the Hamilton 17 total score and the CGI Improvement Percent Responders. So, it may not have been -- because of power considerations, there may not be the opportunity to detect significant difference. But I cannot explain the heterogeneity.

DR. LAUGHREN: If I could just add a point of clarification there, of the two studies that made it overall, that we considered providing the strongest evidence, 004B and 005, it was only in 004B that it failed to make it on the HAM-D depressed mood item.

And even in the supportive studies --

and Joy, jump in if I am wrong -- that those two studies, the centers that made it, made it on the HAM-D depressed mood items.

So, it was really only 004B where it didn't make it on that item.

DR. FRANK: Just sort of a follow up to that, and that was the family practice site; right.

DR. ROBINSON: No, 004B was one of the earlier studies where we used two dose ranges versus placebo.

DR. HAMER: I would like to ask if you have any studies underway now, perhaps with fixed doses, in an attempt to get a better handle on dosing range of dose response sort of effect.

DR. ROBINSON: We do not have a fixed dose study currently in progress. We had decided that we had -- we provided with reasonable confidence that we can define the therapeutic range and the dosing recommendations.

DR. TAMMINGA: Dr. Robinson, there were several questions this morning about bioavailability, pharmacokinetics, and drug/drug interactions. I wonder if you have anything to add to what the FDA said this morning about that.

DR. ROBINSON: Well, I would be glad to

give a couple of points. It has high first pass metabolism. That is not unusual for drugs of this class, but it is high.

I am sorry, you asked two questions and I was --

DR. TAMMINGA: The kinetics and the bioavailability and what data you may have on more chronic kinetics, perhaps the blood level clinical response relationship, if there is any, and then the drug/drug interactions.

DR. ROBINSON: Okay, the blood level data, I briefly summarized, when I answered Dr. Temple earlier. Unfortunately, we only have a small number of patients.

Although plasma levels were drawn during many of the studies as a routine, it turns out that very few of them have much value. It is a small number that have value and you can identify the timing with respect to the last dose.

And one really wants to focus, I think, on the trough levels to try to look at relationships to efficacy.

We found a very weak curvo-linear relationship in those approximately 100 patients where we had documented plasma levels drawn six to

eight hours after their last dose.

So, while it could be argued that scientifically there was a weak relationship, it did not appear to have, because of the high variability of levels, did not appear to have any predictive value.

You had a question, then, of drug/drug interactions. I would be glad to discuss that in detail. I thought that they were summarized, and we could show the formal drug/drug interactions if you would be interested.

There was a small number of benzodiazapines, three in number, were studied. And nefazodone affects the metabolism of two of the three. Alprazilam and triazolam have decreased clearance when given concurrently with nefazodone. Lorazapam appears not to be affected.

The other formal drug/drug interaction studies with haloperidol concurrently given, there there was about a 30 to 40 percent increase in haloperidol levels at steady state, but no effect on nefazodone.

And with cimetedine, which of course, is a drug of great interest because it affects many drugs that are metabolized by the liver, there was

no evidence of interaction with cimetedine.

DR. LAUGHREN: Don, are you planning on pursuing the triazolam or prazalam interaction trying to understand its mechanism better at this point.

DR. ROBINSON: Yes, we are. We believe that it is important to do P450 isoenzyme testing and we are in the process of planning such studies.

DR. HAMER: I am still having some difficulty with the dosing range, inferring a dosing range out of a series of studies in which it appears that a really large portion of the studies, perhaps, were receiving a comparatively low dose.

I mean, usually you would attempt to come out of phase II with a good handle on what the dosing range should be, and then you would attempt to design your phase III trials to span this dosing range adequately.

Here, it looks like you came out of phase II and wound up in phase III with perhaps a quarter of your nefazodone subjects in what you are now considering to be within a reasonable dosing range.

And these are all titrated studies as opposed to fixed dose studies. And then, you are

attempting to infer dose range from that.

I mean, it seems to me not unlikely, for example that, depending on the physician behavior, you might wind up with a fair number of subjects who were increased past what their optimal dose ought to be, in an attempt to get more of a response, and then simply left there, even though they didn't particularly respond further.

I mean, I don't know. I just feel like perhaps I feel a need for some sort of fixed dose studies to get a better handle on dosing range.

DR. ROBINSON: Well, I will try to answer that, if I may, in a couple of ways. First of all, we feel that we showed evidence in three trials that would allow dosing acrose the range to a maximum of between 100 to a maximum of 500 or 600 milligrams. Clear drug/placebo differences on primary outcomes measures for nefazodone.

DR. HAMER: But in terms of the higher dosing range, were those the studies in which you feel now that you attempted to plot the subjects up to the high dose too fast and perhaps might have had a comparatively large number of drop outs in the high dose groups due to adverse effects.

DR. ROBINSON: Again, my opinion is that

that did not occur, at least in two of the important studies. One is 005 and the other is 006, center two, both of which had a rather gradual titration from 200 milligrams a day during the first week, or at the first week of evaluation, to somewhat higher doses over the eight weeks of treatment.

So, we feel confidently that, looking at the complimenting study results, that we have identified a tolerated safe and partially effective starting dose of 200 milligrams a day in the fixed dose study.

And secondly, that in the studies where we had both an active control -- that is, Imipramine -- and placebo for comparison which, in a way, is the most naturalistic study, I think, more consistent with practice, that we showed that the drug was effective and that the dosing range that we recommend is both safe and effective.

There was another point, because I think the fixed dose study design is a very difficult design, particularly in psychopharmacology.

The way that I think about it is that we do believe that mass action is important. We have a lot of focus on plasma concentrations as guides to therapy, although they don't work very well in

psychopharmacology.

If you believe that, and since we know that there is a lot of inter-individual variation in clearance, you would not believe that in a fixed dose design, that all patients randomized to the same dose would be getting their optimal dose.

So, I think the fixed study design is helpful, but it doesn't answer all the questions about how patients should, in fact, be dosed in practice.

I believe that the studies that I mentioned -- 003, 005 and 006 -- are more realistic. And as I pointed out, we saw the highest percent of responders at an end-of-treatment dose of 300, 400, 500 milligrams a day, which is not to say that some patients didn't respond at 200 milligrams, their starting dose.

DR. CASPER: I wanted actually to consider Dr. Hamer's discussion, because if you look at the -- well, what we have evaluated as high dose as up to 600 milligrams, really, if you look at the mean modal dose which was received by the patients, no one really got 500 milligrams. Most were probably just about 400 milligrams.

And the question then is, as you said in

your recommendation, between 300 to 500 milligrams -- the question is really, do you need to go above 400 milligrams.

If you look at the data which were presented, the side effects really increase, there is a relationship between adverse effects and dosing. And so, I wonder whether what we have evaluated as high dose is not really the lower point of the high dose, namely, around 400 milligrams, if the low dose goes up to 300 milligrams. So, there is sort of a medium dose range.

And another question I had relates to the severity of illness in the patients, because if you look at the data, the Hamilton score really indicates moderate depression.

Now, this might not have served your purposes, actually, to have patients with largely moderate depression, because if you want to show an effect, you want to have patients who are more severely depressed.

So, you argue the more severely depressed also improved, but I would warn of -- maybe this is kind of -- I think it really should be taken as a warning.

I wonder whether you really need to

consider doses above 400 milligrams given even your presentation with the 600 milligram data, and whether you don't want to recommend staying with 200 to 400 milligrams.

DR. ROBINSON: I think you have raised very important points, which basically we would agree with. I think when you study a drug over a range, it is important to know that some patients may end up at the maximum dose, however that is defined. We chose to define it as 500 or 600 milligrams.

The vast majority of patients did not go to the maximum tolerated dose, except in the very early phase II, two dose range study, where that was a strategy, because in part, we were interested in efficacy and tolerability early in phase II when we were studying a new and novel antidepressant and we weren't certain how to define the range of interest.

But certainly, I think the point that we can say with some confidence is that those patients who did go to 600 tolerated. There were not alarming safety questions about them. They did not experience unusual difficulties.

But admittedly, there is a bias about which patients get to the top dose.

DR. CASPER: Yes, I would like to emphasize this, because with your design, we don't know whether the non-responders all went to 500, 600 milligrams and whether this dose was even necessary for these people and how they responded in the end, not with this fixed dosage but open dosage design.

You might just have seen higher dosage, but not more of a response, with a little more adverse effects. But still, there is some.

DR. ROBINSON: If I may follow onto your point, which is an interesting one, if you were to do a study, for example, with a fixed dose of 400, 500 and 600 milligrams a day, I believe that it is very likely that what would happen is that you would have an inordinate number of drop outs at the highest fixed doses.

So, the fact that you do that experiment doesn't necessarily help you establish the dose range, because we know that some patients will, by titration, based on their clinical response, should receive a lower dose, and some, a higher dose. And that is the way drugs are generally used for the treatment of depression.

DR. LAUGHREN: But Don, you may have, as you pointed out yourself, have greater success in

doing the experiment if you titrate patients up to the fixed dose. And really, that is the only way you are going to find out what additional advantage there is in pushing patients up to the higher dose.

I don't think you can learn that from a titration design. And it makes it somewhat difficult to write labeling instructions for a drug for which you don't have that information.

I don't think anyone is questioning the finding that you do have efficacy when you titrate within that range. The question is, what additional advantage is there in pushing the dose up to 600. That is not clear from the data that you have.

DR. CHARNEY: Do you have any open label experience on patients that did not do well on the lower doses and were able to be titrated up.

DR. ROBINSON: Well, we have no formal analysis of that. Again, the open trials did allow dosing over the range of 100 to 600, and a small number of patients do end up at the top dose, 600 milligrams, and tolerate it.

So, our belief is that there are not over-riding safety issues for those patients who arrive at the maximum dose by careful clinical evaluation.

DR. CHARNEY: What I meant, say there were patients that went through the fixed dose studies that only got the low dose regimen. Were they allowed to be entered humanitarian studies that allowed them to be increased. Did the non-responders turn into responders.

DR. ROBINSON: Again, we couldn't formally study it because at that time, early in development, there were some restrictions on patients going on into double blind extension for more than a very short time.

DR. TAMMINGA: One of the strengths of this data set in front of us, it seems to me, is the variety of patients that were treated with the drug.

There were both in-patients treated and out-patients, elderly, and the usual depression age range. And even psychiatric patient sets and family practice patient sets.

And there were such differences between the latter two in the 005 study that I wonder what you made of that. I mean, the family practitioners developed such a spectacular drug/placebo difference and psychiatrists were much less able to do that. Do you imagine it was for different patient population reasons.

DR. ROBINSON: Well, I think that is a probable explanation, if one could discern what it is. We do know that the patients who enrolled in the family practice sites tended to have fewer previous episodes.

I have forgotten the other -- there was one other difference of interest. But one might infer from that, that they were less -- there could have been an over-representation of more treatment-resistant patients in those patients that end up at a psychiatric treatment facility. There are, of course, many possible explanations.

DR. FRANK: Have you considered the possibility that the difference was in the clinicians and not in the patients.

DR. ROBINSON: That is a possibility, I would agree.

DR. FRANK: I would suspect that psychiatrists giving placebo probably do something different than family practice physicians giving the placebo. And there were no restrictions on the interaction between the patient and the clinician in any of these trials.

DR. ROBINSON: That is correct, not with regard to time spent with the patient, for example.

DR. FRANK: Or what went on in the interaction.

DR. ROBINSON: Right, and we have some reason to think that there may have been more time spent with the patient, but again, that is just speculation, because we didn't study it -- I am sorry, more time spent in the psychiatric setting with the patients.

DR. LEBER: Just one salvaging comment, that the one thing that we do have in at least a couple of these centers is Imipramine as a measure of the assay sensitivity of the sample. And in that particular study, with the psychiatrists, they may have been able to get a good placebo response but they are unable to detect a difference from Imipramine.

I think that tells you how to weight that study. We have, in general, included these three armed designs, I think a point made by Ms. Mele and by Dr. Laughren.

So, it is a marker for how well the sample responds. We would ordinarily classify such a study as a failed study, rather than as a negative one, because it has, in the words of Modell and Hood, an inability to discriminate a standard drug

from placebo, and so we sort of tossed those.

And that has been our long-standing view. It is not a failure of the drug. It is a failure of the methodology, for reasons unstated.

DR. HAMER: Similarly, did you all speculate on what appears to me to be a relatively large placebo response over the course of the whole set of studies.

DR. ROBINSON: That is always a cause of some consternation when you see it. I guess my own opinion is that, since most placebo controlled trials in depression are, or maybe even have to be, conducted in an out-patient rather than in a really more severely ill -- very severely ill -- in-patient population, that there may be a tendency to enroll more patients who will respond for a myriad of reasons.

There seems to be a gradual escalation of reasons, if you read the literature and listen to reports of other studies with other agents.

I don't think that the placebo response rates that we encountered were particularly out of line with what I understand to be the case with many other studies with other agents in the curing of depression.

DR. TEMPLE: That is my impression, too. One thing that occurs is that, in the setting where there is such a large response in people who aren't given active therapy, it is very hard to learn anything about dose and anything.

What we have encountered recently, having begun depressed people to carry out long-term studies in people who respond and then were withdrawn from therapy is that, ironically, it is somewhat easier to show effectiveness in that setting, because you are only doing it in responders, to people who appear to be able to respond to the drug.

So, a possible way to sort out some of these kinds of things, including dose, is in the withdrawal and maintenance study that you eventually do to randomize people to several different doses and, I would also urge a fair amount of blood level monitoring, including metabolites, to help sort out some of the fairly large number mysteries.

But with the responders, it often turns out it is rather easier to show effect in them.

DR. SCHOOLER: That is very much related to the point that I was going to ask, which has to do with questions of long term treatment, much in

the same way that Dr. Hamer was asking about whether there was a short-term fixed dose study ongoing.

I was wondering what your intentions were with regard to longer term treatment, both in terms of efficacy, withdrawal designs, maintenance treatment, and so forth.

DR. ROBINSON: Well, we do have a formal discontinuation design placebo substitution design, maintenance effect study underway. Those are difficult large studies, take a long time to complete, but we understand that there is value to that approach, and our doing it.

DR. SCHOOLER: Could you say a little bit more about the design. Is that a fair question.

DR. ROBINSON: Well, I think we tried to use what has, so far at least, been the conventional design which, as Dr. Temple pointed out, is to enroll patients who respond during acute treatment who have stabilized their symptomatology by well defined criteria.

Then they get randomized to a placebo or to stay on, remain on, nefazodone on their dose. And follow through to their relapse, again, using well defined criteria and the Hamilton scores and the CGI.

We also have in mind and have, by amendment planned to do, a second re-randomization farther out for those patients who receive treatment, for approximately a year.

DR. SCHOOLER: Do you mean re-randomization to either continue for a second year or be discontinued.

DR. ROBINSON: Or go on placebo. So, again, this might -- I mean, that has value, I think, both in terms of relapse and recurrence inference, but possibly even for as you were asking, for withdrawal syndromes of some kind.

MS. MELE: I just had an additional comment about the psychiatric center versus family practice, and if you are still interested in talking about that, I will just show you.

What I found was a difference between the males and the females in the placebo group, and I thought it was interesting, even though I certainly can't explain it.

On the bottom here are the results for the eight placebo controlled trials, and as you can see, there are essentially no differences between the males and the females.

I just thought it was curious that the

placebo responders seem to be mostly in the female group. You can see that the males are about of the magnitude that we saw in the other studies, where the females are much higher. So, you could probably conjecture a lot of things from that.

DR. TAMMINGA: Do we have any more questions for Dr. Robinson and the company.

DR. HEZEL: Mine is just a real general question. The nine suicides, I have been assured it would be expected in this population. What is the magic number that we wouldn't expect.

DR. TAMMINGA: Maybe if you wouldn't mind, we have our committee discussion after that, and why don't we address to Dr. Robinson the questions we have remaining for him and the company.

DR. TEMPLE: If you discussed this while I was out, tell me and I will find out. The metabolism of the drugs is obviously somewhat complex and there are some interesting drug/drug interactions.

I take it you don't know what P450 isozyme is responsible yet.

DR. ROBINSON: That is correct, we haven't done the studies. We have it in mind to do so.

DR. TEMPLE: Do you happen to know off the top of your head what the isozyme that metabolizes triazolam is. Is it 3A4.

DR. ROBINSON: Triazolam, by inference, would be a 3A4, yes.

DR. TEMPLE: I mean, that raises -- probably everybody knows this, but that raises some interesting problems. If people are familiar with the experience with astemazol and triphenadine know that, so far, only a bunch of antifungals have had profound effects on inhibiting that system, with erythromycin having a much smaller effect.

The magnitude of this is considerable, a four-fold decrease in clearance is quite large, raising the possibility that this agent could interact with quite a few drugs, because 3A4 is ubiquitous and there are many many therapeutic agents that are metabolized that way.

This looks like a fairly large effect. So, apart from triphenadine and astemazol, it is certainly something to think about.

DR. ROBINSON: I agree with that interpretation and we are pursuing that. And because it did raise the very point that you make, we went back to look at the concurrent drugs in the

placebo controlled trials -- I am sorry, in all nefazodone treated patients.

And there were something over 130 patients who received triphenadine, which is one of the drugs of interest, with regard to 3A4 and toxicity. And we did a very careful search of the records of those patients that did not detect any important safety issues.

But again, we admit that is limited data and formal studies still are required.

DR. LEBER: This is another question more for the record. Was there an attempt, in the development program, to look at patients who were thought to be actively suicidal, i.e., in an in-patient setting, in any kind of a controlled way, in response to nefazodone.

DR. ROBINSON: Not in a controlled way. Of the nine suicides, only one occurred in a placebo controlled trial, and that was the patient on nefazodone. Two occurred in active controlled trials, which involved in-patients. And the remaining were open studies in which, when we looked at the records of those patients, several of them were selected by the investigator because, in his or her opinion, they were either treatment resistant or

perhaps more at risk for suicide. But that, again, is by inspection.

DR. LEBER: You may have misunderstood the intent of the question. Maybe I didn't say it plainly. Was there, a clinical trial design to selectively enter patients who were suicidal rather than non-suicidal. And in that trial, were they prospectively randomized to nefazodone and appropriate controls.

DR. ROBINSON: No, it was not. It was an exclusion criteria, as I mentioned, so in the opinion of the clinician if there was significant suicidal risk, the patient was excluded.

DR. TAMMINGA: So, if the committee doesn't have any additional -- Dr. Lin.

DR. LIN: A follow up on Dr. Temple's question earlier. Would you comment or suggest that more studies should be done on drug interactions with drugs or metabolites by 3A4.

DR. TEMPLE: Once you find out what the metabolic route is and how great the affinity is for the relevant enzymes, you can probably make good guesses about where to look for trouble and those guesses should be followed up.

It is not real difficult to do. The

effect is quite large, if it is real, so you don't need a very big study. But this is just a growing recognition on our part, based, in part, that for drugs that are at all close to the margin, the interference with their metabolism can have profound effects. Triazolam is a good candidate for that. So would, I think, be xanax and probably a lot of other drugs.

There is a spectacular interaction, as probably everybody knows, between phloxitine and foroxitine and tricyclics where you virtually, overnight, get an eight-fold elevation of your C max or area under the curve. I mean, it is a really big difference for a toxic class of drugs.

So, the knowledge that these are out there certainly has me nervous. More study seems like a real good idea.

DR. TAMMINGA: Any additional questions for Dr. Robinson. Thank you very much.

Now the committee needs to consider the questions that Dr. Laughren addressed to us initially:

Has the sponsor provided evidence from more than one adequate and well controlled clinical investigation that supports the conclusion that

nefazodone is effective for the treatment of depression. That is the first question.

The second question is, has the sponsor provided evidence that nefazodone is safe when used in the treatment of depression.

Agenda Item: Committee Discussion/Recommendations

DR. TAMMINGA: Dr. Laughren reminded us of a couple of significant issues at the beginning, saying that the results of efficacy are mixed and that there are inconsistencies in the data sets, and then the drug/drug interaction safety questions that we have been discussing.

And then, questions of long-term efficacy and relapse prevention, we have discussed those to some degree. So, the discussion of this drug is now open for the committee.

DR. SCHOOLER: I will start. I had a very hard time this morning keeping the studies, the subparts of the studies, the centers, the doses, the appropriate comparatives, straight.

And I keep finding myself going back to Joy Mele's, one of her early tables on the hand out that we have, which I think lists all of the studies.

And I am still not completely sure that I understand what message we should be taking from each one of these.

One of the things that seems to me is the notion of kind of a box score, like three out of eight were okay, or two out of seven were discounted, and so forth, is a very unfortunate way to look at these data, in part because it seems to me that the early studies were ones which were designed to try to find a way to decide what were the right doses to use and so forth.

So, if I look at that table -- and I would appreciate some assistance because I am still not completely sure I understand it -- it seems to me that the two studies at the top, which were the 003, 0A2, 004 and 005, and the A27, are studies which we ought to discount. You know, I want help with this.

DR. TAMMINGA: Let me suggest a better table, and that is in the brown book that we have, page 48 of Ms. Mele's presentation. That study not only has the studies listed by number -- number 48, tab P.

That has the numbers of the studies and the FDA reviewers' comments and then a one-word

statistical evidence, the bottom line, either failed, supported, positive or negative.

DR. SCHOOLER: Because I guess the question is that if we are saying that the dose is too low, then the fact that the study has failed, it seems to me that that ought to be discounted. At least, I wouldn't necessarily worry about that trial.

DR. TAMMINGA: As I understand, a failed study is not necessarily one where the dose is just too low, but one where there has been no placebo, active drug difference defined.

DR. SCHOOLER: I guess what I am saying is that whatever the technical terminology is, neither of those two studies are of particular concern or interest to me.

It seems to me that if the dose was inadequate, in a sense, you would say that it seems to me you start counting or you start examining the data after you have determined what the appropriate dose range is.

And that is what is comforting to me about those two studies, is that those were early in the development.

So, if we then come down to the next

study, which I guess is the 003 in that series, the problem with that study -- and I would actually like to hear a little bit more about this -- is that three of the centers were -- I guess the word is abject failures in terms of conducting the trial.

In other words, three centers had enrolled 24 patients. And I suppose I would like to ignore those three centers at one level. At the other level, they seem troublesome because I presume that there is a fair amount of experience of the process of selection of centers, so that everybody thought that those were three centers that were a good idea to go with at the outset. And yet, they turned out to provide nothing at all.

I would like to believe that that was purely a function of the three centers. But I would just like some sort of further information that tells me that it had nothing to do with the drug or actually with the design.

I am not sure what to make of that. Now, maybe that was a question that I should have addressed to Dr. Robinson earlier, but as I say, I have had a lot of trouble sorting out of the studies and it wasn't until I got to this point that I have sort of done that.

DR. TAMMINGA: Maybe you could answer that for us. This is about study 003.

DR. SCHOOLER: Right, and the first series.

DR. ROBINSON: That was a purely Canadian study that was done -- all centers were in Canada and we admittedly new somewhat less about the investigators than we would know about U.S. studies.

Our opinion was the same as yours. They were -- those three sites were abject failures from many points of view, and therefore, we then revised the strategy to increase the sample size of the one center where we were very confident that the study was being conducted appropriately.

DR. TEMPLE: Do I understand, Joy, that you actually did an analysis that included all of the patients but didn't do something silly like weighting a very large clinic equally.

I mean, I know there is a long track record of liking to weight equally, which I have never understood, but when you do that you find at least a nominally significant amount, even when you didn't weight them equally, even taking into account that they might have been weird.

MS. MELE: And they definitely were

weird. I mean, there were seven placebo patients in that study who showed a very big increase. In fact, their HAM-D total at the end was about 4.

So, those three centers were definitely strange and the placebo patients in them were also outliers.

DR. TEMPLE: But despite that, I mean, things often look strange when you look at them. Despite that, you did do an overall analysis that included essentially all the patients equally weighted, and the overall result remained favorable. I don't know whether that is additional reassurance or not.

MS. MELE: We did include them and gave each patient equal weight and it was still significant.

DR. HAMER: Did you do an analysis where you just dropped the 24 patients.

MS. MELE: Yes.

DR. HAMER: That was the one we saw.

MS. MELE: That was primarily what I was showing, was dropping those 24, because there was a little discomfort in including a large center with these other small centers.

DR. CHARNEY: My general take on the

drug is that it is effective. However, I am still concerned about the dosage. And maybe Don would want to address it again, because when you look at his table you do see that the 300, 400 and 500 doses do show the greatest response rate.

On the other hand, if you look at what are termed the three positive studies, in two of them -- center two of center 006 and center two of study 005, the modal doses are 332 in study 006 center two, and 347 in study 005 center two, which are clearly at the lower end of what is being suggested as the therapeutic range that clinicians ought to shoot for.

So, I am not clear where, in say, the 400, 500 range of the slide that was shown, where that is coming from, because that is clearly pooled data from, I guess, all the studies.

But when you just concentrate on the positive studies, it looks like a much lower dose would be effective.

DR. TAMMINGA: I had actually looked at the dose that the company was recommending as the therapeutic dose, and they recommend 200 milligrams a day to start with and then an increase subsequently.

So, when I looked at these modal doses, they seemed to be within the recommended dosing range, but I may be wrong.

DR. CHARNEY: Well, it is within it, but I guess in part it is a matter of emphasis when you are saying that it is 300 to 500 that is where clinicians ought to be shooting.

The positive studies, at least two out of the three, suggest it is clearly on the lower end.

DR. HEZEL: Just a follow up remark to that, the clinician won't have access to the modal dose and know that, and that is what you are saying, isn't it, in terms of recommendation, if you recommend starting at 200.

DR. TEMPLE: I know you shouldn't ask questions where you don't have any idea what the answer is. In settings where the time between giving a drug and changing the dose and response is not large, like hypertension, titrational studies have been analyzed using mixed effect modeling, non-mem, and other stuff like that.

To my best knowledge, it has never been applied in this setting, where there is a perceived significant delay between the time you give the

drug.

But that doesn't mean it couldn't be useful if you modeled some sort of delay. And I just wondered whether anybody has thought about that. I mean, I am well outside my competence, but there are lots of people who know how to do these things.

And when all of your studies are titrational design studies and you therefore can't use conventional methods to get dose response out of that, sometimes these things work. They definitely work in hypertension.

DR. LEBER: I have a question to ask Dr. Temple. When you don't know what the lag is between a plasma level and the clinical response, when you have free titration and patients are dosed, perhaps as the curve that Don Robinson showed -- I don't know if you were here -- of an inverted U-shaped response curve -- that is, there is some probability that patients who were totally treatment resistant would be dosed higher.

How will the model decipher or link plasma levels, no matter how many ways it operates, and treatment response when, in fact, you have a bi-variant direction on the response.

DR. TEMPLE: I am not worried about the plasma levels here. The parent and each of the metabolites have not terribly lengthy half lives. So, they ought to reach steady state fairly soon, the parent almost instantly.

What you don't know is the lag between essentially getting the drug on board and a response. On the other hand, you have ways of looking at that, the data themselves. I mean, when do the drug and placebo groups start to separate.

I mean, you get hints of something as little or a week or two and you can, in fact, model those sorts of things and make suggestions about what they look like.

And the inverted U, at least in hypertension, shows up all the time, but when you actually look at the response of particular individuals, they don't show a U shaped curve. They, if anything, keep improving or get flat.

It is only when you look at the population that got the large dose versus the population that got the small dose, that you encounter a population that is highly selective for resistant patients. So, naturally, they don't do very well.

But if you look at individuals, as they are titrated up, you see individual dose response curves. And they generally are monotonically upward. They may plateau, but they go up. They don't necessarily go down.

Now, they could go down but that is a different phenomenon. It is just not very often observed.

DR. LEBER: We really shouldn't be doing this, or maybe we should be, because one of the other things that is going on is that there is a spontaneous remission rate. And I understand there is fluctuation regression to the mean hypertension studies, but there is probably a time trend here that may be strong.

In addition, the outcome measures that we are using in hypertension are probably pretty simple. Although you can find others, you are basically measuring a cuff pressure, and whether you do it with a zero mystifying spignomonometer or not, it is not much of a problem.

In depression, we don't even know which outcome measures are making the change of statistical significance different. In fact, the major problem we have is studies that only examine

differences in P values when they first appear as a measure of treatment onset. So, the question is what should you be tracking and when.

I think it is an extremely difficult area, a very interesting one, but before we ask anyone to do it, we probably need to do a lot of modeling to find out whether it is even feasible yet. I think we ought to, but before we recommend it as a remedy for this, I think there is a lot of work to be done.

DR. TAMMINGA: At this point in time, the committee, however, is called upon to give an opinion on a drug without any of that information. Just like Dr. Charney was saying, the data that we have that relates dose and clinical response is fairly meager.

DR. HEZEL: May I ask my general question about suicide now. What is the magic number. When would I be alarmed. You know, Dr. Laughren, you said that nine is to be expected and I would kind of feel better if they were distributed in all the groups a little bit more.

DR. TAMMINGA: Would you be willing to clarify what the nature of your alarm is. In other words, does the drug cause suicide.

DR. HEZEL: Right, because all the suicides happened in the drug group and if the study sample was randomized, why don't they scatter around in the rest of the groups.

DR. LAUGHREN: Part of the problem is that you are dealing with a much more heterogeneous sample for the nefazodone group than you are for the active control or the placebo, both in terms of cumulative duration of exposure, but also the nature of the exposure.

As I understand it, only one of the suicides occurred in the placebo controlled trials. Is that correct.

And some of the other suicides occurred in open studies in which, you know, if you look back at the histories of those other patients, they had indicators of suicidality at baseline.

I think the most persuasive data set pertinent to your question is the one that Dr. Robinson presented, which is data from control trials, looking at the emergence of suicidality, looking at item three on the HAM-D, where you don't see any difference across nefazodone, active control and placebo with regard to emergence of suicidality.

That is the only data set where you have

enough similarity across the treatment groups to actually make a comparison, and that showed no indication whatsoever of any differentially greater suicidality for nefazodone compared to active control or placebo.

That is what I find most persuasive here. I don't think it is even -- it is very difficult to try and interpret this finding of nine suicides across 3500 patients exposed to nefazodone across a very diverse clinical trials experience, and the fact that there are none occurring in a much different population of placebo and active control patients.

DR. FYER: I don't disagree with your basic premise of it not being an alarming number for this kind of trial but I wonder a couple of things about it.

First of all, I think I would be a little hesitant in a study that, as a treatment entry criteria, required that people with a significant amount of suicidal ideation were excluded, to use the treatment emergent suicide symptoms.

And I wonder if what might not be more convincing would be for that table and maybe some

additional clinical material to be more generally distributed.

That table describes when people committed suicide. I notice a lot of people on that table, it was seven to fourteen days after their last study visit, about half of them, which might suggest some other kind of process going on in terms of suicide.

DR. LAUGHREN: Does the company have a slide of that table that you could present so that everyone could look at it.

DR. FYER: I am not disagreeing, you know, with the substance of your remarks. I am saying, in this kind of a situation where the group data is so difficult to interpret, some more detailed clinical information about the cases might actually be more helpful.

DR. LAUGHREN: That is what available on this slide if you wanted the committee as a whole to see it.

DR. FYER: I think in these kinds of situations maybe distributing that with the other data might be useful.

(Slide is shown.)

DR. ROBINSON: This summarizes some of

the relevant data on the nine suicides. As Dr. Laughren said, some of the suicides occurred, as you can see, if you look at the days on treatment, in the first weeks of treatment, but then they are distributed out to as far as 366 days.

As I mentioned in response to Dr. Leber's point, at least three of the outpatients were selected by the investigator in open trials because they had been treatment resistant and these patients often had a history of previous suicide attempts.

As you can see, two of them occurred in an in-patient setting, they actually occurred in a hospital. So, we didn't discern any real pattern of this, except to say that it is a rather heterogeneous group and it occurred over an extended period -- it was distributed throughout a rather extended period of treatment.

DR. TAMMINGA: Dr. Hamer, do you have questions on this slide.

DR. HAMER: No, not on this slide.

DR. TAMMINGA: Are there any other questions or comments on this slide.

DR. SCHOOLER: I might just mention that there is one consistent feature, and that is that

eight out of the nine are men.

DR. TAMMINGA: And what are we to make of that.

DR. SCHOOLER: I haven't a clue, just that it is a consistency.

DR. TEMPLE: It is at odds with the distribution of patients, who are two thirds, or sixty percent, women.

DR. FRANK: And it is not simply a canard, it is an actual fact, that depressed women are more likely to attempt suicide, but depressed males are more likely to complete suicide. I mean, there is actual data to support that. So, this is consistent with the epidemiologic data.

DR. TAMMINGA: If there aren't any more comments on this slide, then we will have this slide off and the lights on. Do you want to ask additional questions or comments on the suicidality issue, Dr. Hamer.

DR. HAMER: I also want to sort of agree with Dr. Laughren. What we have got here is a placebo group that is at least three to four times the size of any of the other groups.

So, if you divided the number of suicides -- excuse me, we have a nefazodone group

three to four times the size of any of the other groups. If we divided those nine suicides by three, that is three suicides. Divided by four, it is two-and-a-quarter suicides.

If we had one suicide in any of the other groups, we would have almost the same suicide rate. Two suicides in, let's say, the tricyclic group would have probably a slightly higher suicide rate.

So, we are operating in the area of very low numbers, where it only takes one additional subject in one of the groups to do something to completely change the results. These are very unstable estimates.

And that is the reason why I am not overly worried about the nine suicides in a group that is three to four times as large, minimum, of any of the other groups.

DR. TAMMINGA: Do you think we ought to address any additional suicidality concerns that you have, or any of the other committee has now, or consider it a discussed issue.

DR. HAMER: Just one other comment, in a clinical sense. These are patients, in a sense, at high risk for suicide. If you look at the lifetime

prevalence, yearly prevalence, yearly incidence of suicide attempts and all that kind of stuff, I think it is remarkable, in a way, that we don't have more suicides all over.

DR. TAMMINGA: If that issue is done, I think one of the things that the committee has to consider is a return to Dr. Charney's issue about having an opinion on efficacy in the face of the dosing information that we were given by the company. And perhaps other people have additional comments on that.

We are not called upon to recommend further studies. We are called upon to recommend our current opinion today.

DR. HAMER: To address Dr. Charney's question, I will sort of note once again that to some extent, this is a problem with the structure of the question that we are given to decide and which has to do with, I guess, the way that the regulations are written.

That is, the company was asked to provide us with evidence of two studies which are well controlled and well designed, that provide evidence of efficacy. And the regs were not written to say two out of two studies or two out of four

studies or two out of five hundred studies.

So, I am always puzzled by -- was it you who said the ballpark figure, you know, the box score figure. You know, it is easy, when you have got two studies or three studies and two of them show efficacy.

It is harder when you have a larger number of studies and things are mixed and really, the question we are asked to decide, in a sense, doesn't specify out of how many studies. It just says, were there two studies.

DR. TAMMINGA: Well, we are not morons.

DR. HAMER: I am not saying that. All I am saying is that the structure of the way that -- my impression is that the structure of the way the rule is written makes it hard for us to do our job.

DR. LEBER: Let me emphasize something. It says that there has to be evidence that comes from adequate and well controlled investigations, including clinical investigations -- there is an s at the end. And we have said that usually or ordinarily means more than one.

But what has to come is evidence that would allow qualified and appropriately qualified experts to conclude from the evidence -- and I think

that means the evidence as a whole -- that the drug has the effect claimed for it.

So, that gives you great latitude in interpreting the entire data set. I think technically, if you had only one open study that showed hope, we would say that you could not conclude from the evidence.

But given a body of evidence arising from adequate and well controlled, it is your judgment -- we need to know how you arrived at it, that you have got to put plainly on the record, but we need to know whether the evidence that you are reviewing as experts with knowledge could reasonably and fairly conclude from that evidence that the drug has this effect as an antidepressant.

DR. TEMPLE: Various of you were getting at how one gropes with that. If the dose, in retrospect, turns out to be too low and a study fails, you are not particularly worried about it. If you include your active control and it fails, you are not too worried about it.

You are more worried when, seemingly, the same experiment doesn't work once and then doesn't work another. Those points of confusion are no problem.

But you can bring whatever reason to this you feel you want to. It needn't be mindless. The only limitation is we generally expect replication. But that doesn't mean that if you get two studies out of four that work, it is okay.

DR. TAMMINGA: We hope that it is not mindless. In fact, from that point of view, only the 004A actually has been rated by the FDA a negative study. And all of the other studies that weren't positive were actually failed.

There is only one negative study in this data set, as I read it. And that is, 004A is a negative study. And the other failed studies are studies where there has been no difference defined between placebo and the active control.

DR. CHARNEY: Yes, it is that data that leads me to say that I think it is an effective drug. But I do worry about the large number of failed studies. And when we address the issue of what may account for that, we really don't have data that says, well, it failed because this is the patient group that was enrolled, it failed because these are the sites that conducted the studies.

And that is, I think, in part the uneasy feeling that at least I have, because of so many of

the failed investigations.

DR. CASPER: I would also agree that basically we have drug rates with moderate effectiveness, because of course, it is tried -- if you have a drug that is not fully effective, you try to increase the dose, and this was done in many of the studies.

But we don't really know whether the increased dose really had more of an effect, most likely, given the data that we have now.

If we were recommending studies to the drug company, I would recommend that we look at the patient population who really did respond to this drug, and try to identify better the particular either the symptom constellation or the patient population who did respond.

But we do not have overwhelmingly strong support for this drug being a strongly effective antidepressant.

We have -- and I would agree we have some effectiveness, and it is moderate.

DR. HAMER: That is right. We have seen the slide which shows, of the people who were on various doses, what proportion of them responded. It might be instructive to see a slide of, of the

people who responded, what doses were they on. I don't suppose you have that.

DR. CHARNEY: I think there is another way of asking the question. If we saw a distribution of the patients who responded in study 006 center two and study 005, center two, where the modal doses were 330 and 340, what if that data -- maybe if you have it, it would be good to look at it -- what if that data showed that there was a fair number of patients that responded at 200 milligrams in that study, and it was equal to the number that responded at 300, would you then consider the low dose studies as failed studies or negative studies.

DR. TAMMINGA: Well, the failed studies were not just where low doses did not produce a significant change. The failed differences were where there was no difference between placebo and active drugs.

DR. CHARNEY: But they were called failed as opposed to negative because it was interpreted the dose was too low.

DR. TAMMINGA: No, because there was no difference between active drug and placebo.

DR. CHARNEY: But you would have called it a negative study then. But you called it failed

as opposed to negative.

DR. TEMPLE: It is both. Some of the low dose studies didn't have Imipramine and were considered failed anyway because the dose was too low.

DR. CHARNEY: It is stated right here on page 48 at the bottom. Is that data available, to look at the distribution of doses in the patients in the positive stuff.

DR. TAMMINGA: Response by dose in center two and center two of 006 and 005. Let's give the company just a minute to do that.

DR. TEMPLE: Didn't they do that in that cumulative response thing.

DR. TAMMINGA: Let's let Dr. Robinson respond to this issue in general or in specific.

DR. ROBINSON: We do not have that analysis by individual study, in part because it is very difficult to tease out dose response relationships except in larger samples or meta analysis or grouped analysis.

So, the slide I showed was our effort to establish the end of treatment doses and the probability of response in those patients.

In general, I think we have established

that 200 milligrams -- in those studies where the starting dose was 200 milligrams, where there was an active and a placebo control in addition to nefazodone, that nefazodone was effective and that the drug should be titrated based on clinical response.

And as you will see from the various tabulations and graphs, on average, the modal dose on average was in the range, for those later studies, of 300 to 400 milligrams, approximately.

So, I think it is the best one can do to bracket a therapeutic range.

DR. LEBER: This has to do only with terminology and I think we ought to be careful. The words failed and negative are thrown around. They don't have an official meaning for us, although that doesn't mean that we haven't attempted to separate the two.

This is in the past. When we have had a trial that includes an active treatment arm, when we were able to find that we cannot discriminate the active treatment arm, find no difference between it and placebo, we have used the argument that we know, in the sense Modell and Hood used the term assay sensitivity, that that study can be disregarded,

because it documents whatever the reason is that that particular set of circumstances couldn't discriminate drug and placebo, and we discount such studies.

In the setting where you believe that you fail to find a difference because the dose is low, you can't be absolutely certain that is true if you find no difference, without that sort of marker for effectiveness.

So, we have been more cautious there, although people will argue, post hoc, from other priors that a particular dose is too low to show an effect, you don't really know that.

So, I just wanted to clarify the use of those terms very precisely.

When we say, now, a failed study, we usually mean an active control. It is not discriminated from placebo.

DR. SCHOOLER: But that is not the way that that is used in this table.

DR. LEBER: I understand that. I just want to put for the record what we mean.

DR. SCHOOLER: I guess the question has to do with the dose and the response. And one of the things that can't be separated is whether the

300 to 500 dose is effective simply as a function of time, because that is the end point dose, and perhaps the person would have gotten that level of improvement if they had stayed on the lower dose, since there is a full mix-in of time and change in dose.

And that is a concern for me because, in proposing a starting dose of 200 milligrams a day that would then be titrated up, the titration would, in a sense, be occurring before one had an opportunity to wait and see whether the 200 milligram dose was effective.

If the titration takes place trying to minimize side effects and keep patients comfortable, then you would probably be seeing the titration within a week or so, which I think we all feel is too short a time to know whether the drug is working.

DR. LAUGHREN: You do have several studies here which compare low and high doses of nefazodone, where patients are titrated over a period of six weeks that show an effect for the high dose but failed for the low dose.

DR. SCHOOLER: But where the high dose is not administered at the upper level of the dose,

as Dr. Charney has suggested, that the dose seems to be at the lower end of that range. Is that fair.

DR. LAUGHREN: It is certainly higher than the lower dose.

DR. SCHOOLER: Higher than the 200 perhaps. Let me see if I know which study we are talking about. This would be the 004B. Is that the study that provides that information.

DR. LAUGHREN: Yes, that would be one such study.

DR. SCHOOLER: Okay, what would the other one be.

DR. LAUGHREN: Well, 003 had two different doses and, correct me if I am wrong Joy, but the low dose certainly failed in that study. The high dose succeeded, at least on the last observation carried forward.

DR. TAMMINGA: So, we essentially have a low dose range and a high dose range with the actual doses for the high dose range on the lower end.

DR. LAUGHREN: Right.

DR. LEBER: I think if you look at Joy Mele's last slide, you see the confounding of dose with the titration schedule. And I think that was the point that Dr. Schooler was making, so that you

can't tell, you can't distinguish dose from the way the drug was induced, if you will, and that may lead to all sorts of problems that are beyond interpretation.

DR. TEMPLE: But as Tom said, the attempts to use still lower doses, I mean, they were up to 300 but in fact nobody, most people, didn't get to 300 there either, do give some reason to think that continuing to give 150 or 200 probably won't do it and that you need to be shooting for something higher.

So, there is partial confounding of duration and dose, but you do have some information about the very low dose.

DR. TAMMINGA: Additional efficacy considerations.

DR. FRANK: One thing in trying to understand this that hasn't been clear to me so far is, in which of these studies in-patients that were included, whether there was any study that was exclusively a study of in-patients and whether the in-patient and out-patient data have ever been considered separately.

MS. MELE: There were no in-patients in the studies that I talked about this morning, but I

did look at the two in-patient studies that the company submitted.

One of the studies was of the very low doses. It was very early fixed dose study of 75, 150 and 300 milligrams of nefazodone. There was no placebo group in that study. And it was only of a four-week duration.

The responses on the drug in that study was about -10 on the HAM-D 17.

DR. FRANK: For all doses.

MS. MELE: For all dose. There was no dose response. In fact, I requested the data for that study from the company and I tried some dose response analysis and found no relationship at all between dose and response.

Secondly, I looked at another in-patient controlled study. It was active control. The active control was chlomipramine, and the responses on chlomipramine were a little bit higher, but both of them showed an appreciable change on the HAM-D 17.

Those were slightly longer studies of about eight weeks duration. Slightly more patients on nefazodone dropped out due to efficacy than on chlomipramine. But still, there was really no

appreciable difference between those two drug groups.

DR. TAMMINGA: Is that second study, is that what the nefazodone dose was about.

ME. MELE: I don't remember. The was the 006 study. Perhaps the company knows the dosing of that.

DR. ROBINSON: The dose range was the same, 100 to 600 milligrams with titration.

MS. MELE: The end point mean modal dose was 480.

DR. FRANK: But as I understand what you are saying, there was no placebo controlled data for in-patients.

MS. MELE: That is right. In those two studies, there was no placebo.

DR. LIN: I just wanted to say that I share the confusion of many of the committee members in terms of the efficacy of this drug. But one thing that is comforting is this last-to-the-last slide presented by Ms. Mele.

According to this, the studies that did not show efficacy also showed non-efficacy in terms of Imipramine effects, or there is one that didn't have Imipramine there. So, the majority of the

studies actually indicate efficacy of the drug.

So, I would think that this clearly demonstrated the effectiveness of the medication.

In terms of a dosage, I think that if we look at the last slide of this package, it does show that two of the studies that were effective had a modal dose of around 300. So, that means that some of the cases responded to the treatment above 200.

So, I wondering maybe, in light of that, in the labeling and package on page 16, instead of saying that these studies indicate that most responding patients received a daily dose between 300 to 500 milligram, whether it might be more accurate to say that it is between 200 and 500.

DR. CHARNEY: I was just going to say, we don't know that because we haven't seen the distribution. We don't know how many of those patients in the positive studies responded below 300.

DR. LIN: That is true. I am just guessing that in general, if the model dose is, say, around 325 or 350, you would expect 20 or 30 or 40 percent of them below 300.

DR. HAMER: That is really the slide I was asking for earlier. Of the patients who

responded, how many were taking 200, 250, 300, 350, et cetera, et cetera, et cetera, to get an idea of the distribution of the dosages among the patients who responded.

DR. TAMMINGA: Although that would be a step beyond the dose data that we have now, it still wouldn't be uncompromised dose finding data. I think what we would really like to see if we could, would be a fixed dose study with an analysis of what patients responded on which dose.

DR. HAMER: That is right.

DR. TAMMINGA: But this is the hopefully the beginning of studies with this compound.

DR. HEZEL: Did you collect compliance information on any or all subjects to determine if they were taking the drug.

DR. ROBINSON: It is standard practice in clinical trials to make very careful accounting of the prescribed dose, the amount taken by pill count and so forth. So, as good as it is possible to establish compliance, I would say that a very strong effort is made to show that, in fact, the patients were taking their medication.

DR. HEZEL: By pill count.

DR. ROBINSON: By pill count, yes.

DR. HEZEL: So you have the patient bring the bottle in and count pills.

DR. ROBINSON: That is correct. They are accounted for and they are counted.

DR. HEZEL: When did you do the plasma studies for the different studies.

DR. ROBINSON: The plasma concentrations, they were done throughout many of the studies, actually, but as I indicated, it is very difficult, in a clinical trial, to collect well documented plasma level data.

And when you select the ones that are properly documented and also fall within six to eight hours of the previous dose, it turns out to be a relatively small sample.

We looked at those approximately 100 patients where we had that information and we, as I pointed out, did see some evidence, although very modest, of a curvo-linear relationship.

And we also saw evidence that plasma levels, on average, correlated with the dose that the patient was taking. So, there was some correlation with dose and plasma level.

But there is a great deal of variability in the data. So, there is a big variance term with

those.

DR. TEMPLE: There are available better ways to really find out what people take. There are smart bottles and things like that. I think there is a fair view -- perhaps promoted by people who sell smart bottles -- that pill counts are not really the best way to find out what a person is taking.

So, it is possible to do better. Whether that would be too costly to apply to every study or not, I don't know, but the technology is actually available for actually timing -- it also helps with your blood level measurements because you can tell approximately what time the bottle was opened and presumably that has some relation to when the pill was taken.

DR. HEZEL: Well, that would make me feel better because we know that just compliance in general in the general population is pretty poor. So, we are asked to answer these two questions on the assumption of 100 percent compliance.

DR. TEMPLE: No, I mean in general, poor compliance tends to screw up studies. So, you could argue that you are looking at a worse case here, that if compliance was better, they would do better.

In general, that doesn't make the studies work out better and may account for some of the reasons that studies don't work -- poor compliance, particularly with a drug with some side effects.

It shouldn't give you a false -- if you think these are great data, that is probably not because of the compliance. Bad compliance interferes with the results.

DR. FRANK: I was just wondering whether anyone thinks this is a compound for which stability of level dose ratios would be an important indicator of compliance, and whether you have that data.

One of the ways that one sometimes looks at compliance over time is stability, a ratio between the blood level and the dose. How much does that change over time.

Now, obviously these are pretty short term studies, so that may not be as meaningful.

But I was wondering, in the small set of data which you have which you feel is worthy of looking at, if you have looked at level dose ratios.

DR. ROBINSON: No, we haven't. Again, it is a good question, but it is very difficult -- it is hard enough to get data that is well

documented, when it was drawn in relationship to a dose and a rating.

It is very difficult to get paired data now over time. But we have no reason to believe that the plasma concentrations change in a way other than you may expect, given the pharmacokinetics, which has been discussed.

DR. LEBER: Again, I think this is a complicated situation. I think the firm only recently discovered the dione was active. So, you really haven't done measurements of that.

It may have saturation. So, once you reach a certain dose, I believe -- and my colleagues in biopharmaceutics can correct me -- doesn't the dione saturate out so that, no matter how high you draw the dose, you tend to get a fixed level of it after a while.

And then there are other problems in the relative ratios of the hydroxynefazodone and the parent. And I don't know how many of these have been measured or are useful at the present time.

DR. TAMMINGA: It seems to me that it is the sense of the committee that this is a drug that shows effectiveness in the treatment of depression, but there is a considerable uneasiness about which

doses show effectiveness. And perhaps we could focus on this discussion so that we could render our opinions in a timely way.

DR. HEZEL: One of the hardest things for me, the questions we were asked to answer are very specific. But in practice, the label generalizes to a much broader treatment and dosage, actual use.

So, I feel like, by voting one way or the other, I am answering specific questions that then are extrapolated, in labeling, to much broader use and practice.

DR. TAMMINGA: I think what we are being called upon to answer are questions of safety and efficacy, and we are not necessarily being called upon to review labeling, although I guess that our comments on dose range would be welcome.

But it is not my impression that the indication is broadened by the labeling. I think we are being asked to comment on a labeling for depression, for the treatment of depression, and that that wouldn't be broadened.

DR. LAUGHREN: Yes, the general questions are effectiveness and safety of the product. Labeling generally comes later. We

certainly wouldn't mind any general comments that are pertinent to particularly important aspects of labeling.

In writing labeling and improving labeling, we certainly try not to let the labeling to extrapolate beyond the data.

DR. HEZEL: I guess I wasn't clear on my point. We are asked to answer those two questions given these two very limited pieces of information, but the general practitioner, consumer -- being patient or physician -- doesn't have access to make those same judgments. But in use, that is what happens.

DR. LAUGHREN: FDA doesn't regulate the practice of medicine. An individual clinician is not limited by the labeling in what he or she chooses to prescribe the drug for.

DR. HEZEL: But the label is the most common piece of information will have available, not all of this data.

DR. LAUGHREN: Well, we try and include all the pertinent data that would help a clinician in prescribing in the label.

DR. TEMPLE: See if this helps. We approve drugs when there is evidence of

effectiveness and where it appears that they can be safely used and when it is possible to describe, in labeling, an approach to using the drug that will accomplish safe and effective use of the drugs.

If this drug had bizarre side effects and you couldn't figure out how to administer it in such a way to prevent them in a reasonable number of people, so that you thought the relatively poor dose response work up we have seen here really gets in the way of using the drug safely and effectively, you might well advise us that we can't write adequate directions for use.

On the other hand, lack of good dose response information may induce a certain clumsiness into this. You may have to start titrating way below the level where you really would have to if there was better dose response information. Maybe you could skip right to 300 if this had been assessed properly.

You could conclude from that that, while more information is welcome, you actually can write a dosing regimen that a practitioner can use to get to the right place. And teasing out, you know, which of those two things it is is really part of what we are asking you. I don't know if that helps

or not.

We do care about being able to write adequate directions for use. Sometimes they are the devil. I just went back to look at desipramine labeling. It says, start way down here and go way up here. That is because that is the only way that anybody knew how to cope with the fact that there are two populations, some of which get a big amount of drug and some who metabolize it differently and get a much lower amount of the drug.

So, it was very crude. Really, the right way to do it is find out whether a person is a slow metabolizer or fast metabolizer and adjust the dose. But I don't think people knew that when the labeling was written and it is sort of clumsy to do it now.

But if you felt that the lack of knowledge really interfered with being able to use the drug properly, you should tell us that, and that would matter.

DR. TAMMINGA: I would like to know what the summary of the committee is on Dr. Temple's last comment, whether we feel that there is enough evidence, based on the studies that have been done, to use the drug properly, maybe not exactly, but at

least properly.

DR. FYER: In response to Dr. Temple's statement, I have some reservations related to Dr. Hezel's about the sort of all or none quality of the decision that the committee is asked to make in terms of advising you.

And one thing that I think helps me with that has to do with being able to discuss labeling, because labeling is the most influential thing in clinical practice, hopefully.

For example, in the drug that we are considering today, I agree with you about the seriousness of the issue of potential interactions. And combined with the question about whether such high doses are really necessary, in several recently-approved drugs, the initial dosing instructions have turned out to be much higher than what was actually finally needed.

Now, if those drugs had had the kinds of interaction that this drug seems to have, we might have had a lot of very serious medical events completely unnecessarily.

For example, on this drug, I would feel much more comfortable if we could say, well, it does look to me like this drug was probably effective, if

we assume that the studies were low doses, or argue the dosing rather than a negative study.

But if the labeling were to say to people very strongly, up front, look, this is a drug where there may be serious interactions with commonly used drugs like benzodiazapines, rather than bury it away someplace, that would make me incline more toward advising them toward efficacy, than in the current situation where it is not clear if we have any influence on labeling and, if so, it is going to be in a standard way, even though we know the situation is not a standard one.

DR. LEBER: I think that is a very eloquent statement and I think we want to hear what you want to say about labeling and every thought that would mitigate the risks of the drug and lead to its proper use.

But for the decision making process, it is useful to find -- parse out if you will -- why you conclude it is or is not effective in use. And that might be part of an issue of for whom.

For example, Dr. Frank has asked on one or two occasions the nature of the population. Are they bipolar Is and bipolar IIs. How depressed is the population -- severity issues. All of that can

come out in labeling.

How we emphasize labeling and other issues, we certainly want to hear. I think what we said at the beginning, when Dr. Laughren spoke, that he didn't want to discuss labeling per se, it is because we really have not, as an institution, reviewed the company's draft labeling at this point.

It wasn't to discourage you from offering us good advice about how the drug should be labeled. So, I want to erase -- if we got you off on the wrong foot. That is not our intent. We need to know anything that we can that would make it a safer and effective drug when used. So, your advice is welcome. We just didn't want to get into the nitty gritty of negotiating the words about how we spin something, which is probably what we often do in the very end. So, what you say is heard and listened to.

DR. TEMPLE: Just specifically, the one identified interaction with triazolam is fairly obviously quite important, and really affects whether you should decide to use those two drugs together. We would certainly feature that prominently. Whether we know other things that we know well enough to feature prominently or whether

you end up saying, well, there is all this stuff we don't know, that is trickier.

But we are very conscious of metabolic interactions these days. We have had a number of exciting experiences related to it.

DR. CASPER: I think we are in a dilemma and we have talked about effectiveness -- I don't think we can talk about effectiveness in a general sense, because we can only talk about the effectiveness of the drug in relationship to the data we have seen here.

And the data we have seen are largely out-patients. There is no placebo controlled in-patient study. The data we have seen are moderately depressed patients, moderately depressed out-patients. And the data show us that there is an improvement which is also moderate, an improvement from a HAM 25 to, off about 10, gets you still to a HAM 15 or 16, which means you are still depressed, and this after six or eight weeks.

So, what we have seen, I think, and not considering the dosage problems, whether indeed, an increased dose is more effective, which most clinicians actually assume, I would say the drug is effective in out-patients, is moderately effective

in out-patients in low to moderate doses.

And I would want to qualify my recommendation about the effectiveness of the drug, limited to those conditions.

I think the issue raised by Dr. Fyer about the drug/drug interaction at high dose, I think, is a real one. I think labeling informs physicians, or physicians need to be informed. And labeling does inform physicians.

And if we would say, this drug can be used in high doses, the high doses more effective, as the data were presented to us, I think it would be unconscionable to do that.

DR. TEMPLE: We would certainly try to describe what can honestly be said and what can't. Let me ask you a follow up.

Typically in the indication section or sometimes in the clinical pharmacology section, we described who the population that was studied is and what was found. And, for example, it would come and we would say, there were no placebo controlled trials in in-patients. That is typically how we convey that.

We wouldn't usually say, don't you dare us it on in-patients. That seems to go beyond what

the absence of data would require, although we are certainly prepared to hear suggestions to that effect.

We ordinarily try to describe the providence of the data, why do we think it works and who do we think it worked in.

DR. LAUGHREN: Just a follow up on the point Dr. Temple was making, I think it is important to keep this in context and look at the other antidepressants that we have approved in recent years.

For the most part, we don't have in-patient data because of the difficulty of studying in-patients. And as Dr. Temple pointed out, our usual approach to conveying that information is not to limit the indication but describe the populations in which the studies have succeeded.

And if you have heard of some particular problem with this drug that would merit a specific indication, that would be one thing. But I think it would be a clear departure from our usual approach to try to limit the indication in some way.

DR. CASPER: I did not mean to say that, because I think what I said is that we can only describe its effectiveness in those populations. I

did not want you to limit the indication, because I agree with you. I think, actually, this drug might be more effective in in-patients, but I don't think we have the data for it.

So, I would not want you to limit the indication, but I don't think I could say anything about the effectiveness of the drug without seeing the data, in in-patients.

DR. LAUGHREN: Right, and our labeling would convey the fact that it has not been adequately studied in in-patients.

DR. CHARNEY: It is true that it is hard to study in-patients in placebo controlled studies. But it is not hard to have studies in which you have a comparator that is also active.

I think it would have been useful, and I would recommend for future antidepressants, to have a comparator study in severe in-patients so that at least you can show it as as-effective.

If we had a study -- I think we have it but we don't have the data -- that shows that it is equally as good as menafronil, chlormipramine or other ones, then you become a little bit more comfortable in the idea that this would be used on in-patients.

DR. TAMMINGA: I think we do have that. I think was one that, if I am not mistaken, Ms. Mele showed before.

DR. LEBER: I think you are raising a question that I would like to re-surface again, and that is that the failure to find a difference between two treatments in an in-patient study, even one which shows improvement in the patients, is ambiguously interpretable.

It may, in fact, be a drug effect equally in both treatment groups. On the other hand, it might be the asylum effect, coupled with just good therapy. And that is part of the problem here.

And priors are not always as useful about the distribution response in hospital. You really don't know if there is assay sensitivity.

DR. CHARNEY: I think that is true, but if you have a negative result, if your drug is doing worse than the comparator, then that is a red flag.

DR. CASPER: If we are to design a study, I think ideally we want to have an inpatient study of a fixed dose, or a couple of fixed doses, placebo and active control, and plasma levels.

Plasma levels, not initially, but after

the fixed dose is reached for one week. So, ideally, we would like to see if we could recommend this for future studies.

DR. TEMPLE: That sounds good and it is exactly what we would like to see, but the context is difficult. Historically, we have had difficulty getting placebos to be used in depression trials at all. The Europeans, for years, wouldn't allow such a thing because of fears of suicidality. Only very recently have they even tolerated such trials.

So, we have insisted on them for out-patient settings, but for the more severe, more suicidal people inside, we have had a lot of trouble getting those trials. But we welcome the support for it. Maybe it can be done again. We can watch people inside. You would think it would be safer.

DR. LEBER: And I think we have been fairly reasonable in accepting other kinds of outcomes, like time to forced withdrawal from a study because of therapeutic failure. The distribution of those times can show drug effect in an in-patient study.

The amount of rescue medication being used, a variety of other indirect indicators of an effect which we might use as the primary proof of

the effectiveness, but would give a lot of comfort about whether or not the drug is working in the population.

DR. TAMMINGA: I am trying to keep track now of who all has actually expressed their opinion on out bottom line question of efficacy.

DR. SCHOOLER: I don't think I have. I would say that I would agree with the majority of the group so far, that the drug is effective. I think, though, that I share the malaise that I am hearing around the table.

People keep wanting to qualify the term and I would qualify it in a further way, which is that the general experience -- in a further way talking about the duration of the effect, in that we have very little information beyond the discontinuation for lack of effectiveness in the double blind extension regarding long term treatment.

I am comforted by the fact that there is a long-term discontinuation trial that is currently ongoing. But it is certainly my impression that six or eight weeks does not represent the limit to which antidepressants are administered. And the kind of bail-out which says, re-evaluate before going

further is a sort of restricted one.

But I appreciate the situation that we are in and I would say that I vote for effectiveness.

DR. HEZEL: I will have to abstain on the question of effectiveness because, although the sample size originally was over 2,000, ultimately the number of responders was fairly small, the lack of compliance information, unclear dose response information and the lack of long-term treatment info.

DR. TAMMINGA: Let me just see if everybody has expressed their opinion that they would like. If we could take a vote on the question of efficacy.

Has the sponsor provided evidence for more than one adequate and well controlled clinical investigation that supports the conclusion that nefazodone is effective for the treatment of depression. All that would concur with that, please raise your hands.

(All but one hand raised in concurrence.)

DR. TAMMINGA: All opposed.

(No hands raised.)

DR. TAMMINGA: And all abstaining.

(One hand raised.)

DR. TAMMINGA: Let's turn to the next question of safety. Has the sponsor provided evidence that nefazodone is safe when used in the treatment of depression.

DR. CASPER: Since we are proceeding swiftly here, I think there is good evidence that the drug is fairly safe. My concern would be with drug/drug interactions. The drug might interact with other drugs which are not safe. Therefore, the drug might be compromised at high doses, if the enzyme systems are occupied by other drugs.

So, I think the nefazodone itself is, I think, can be considered a fairly safe drug.

DR. TAMMINGA: Safety issues that people would like to discuss.

DR. SCHOOLER: This is back to the slide that Dr. Robinson presented on common adverse effects. The nefazodone column includes all of the nefazodone doses, and I would be interested in seeing a column that looks like that, but which dealt with the higher dose group, or at least separated the doses, because I think that that would be a more valuable piece of information to have,

because it might more closely match some of the dosing recommendations.

That column includes some that are nefazodone 50 and 100 in those.

DR. TAMMINGA: You would like the committee to see that or you would be content if the company showed it to the FDA along with their dosing.

DR. SCHOOLER: I am more than happy to have it shown to the FDA, rather than to the committee, but I think it is an important added piece of information.

DR. CHARNEY: I guess I would feel comfortable in saying, when used alone it is safe. But at this point, putting it out on the market and leaving it up to the clinician without more control data on the true extent of the interaction, particularly with the benzodiazapines, I am concerned about that, because so many of these patients are on benzodiazapines.

What is going to be the clinical meaning of the drug/drug interactions. So, I would recommend further studies be completed and examined.

DR. TAMMINGA: When the FDA wrote labeling, the actual data that the company already

has with the three benzodiazapines would specifically be included; is that right. So, that they have actually done drug/drug interactions with three different benzodiazapines.

DR. CHARNEY: Was that the behavioral data. I may have missed that. But in terms of, if you put a patient on .25 of triazolam and they are maintained on nefazodone, what happens to that patient.

DR. LAUGHREN: There were pharmacodynamic effects as well, in that interaction study. I forget the exact tests that were done, but clearly, there was a greater effect from triazolam along the same lines of somnolence.

DR. CHARNEY: So, when the clinician reads the package insert, are they going to know -- what is the safety threshold there.

DR. TEMPLE: They are going to know not to take those drugs together, because the right dose of triazolam to take with this drug hasn't been defined. It is probably not even available.

DR. CHARNEY: So, you are saying, do not use these drugs in combination.

DR. TEMPLE: That is my reading, at least initially, because you can't easily take much

less than .125, and if it is bouncing it by a factor of 4, you can't get there.

DR. TAMMINGA: And there are benzodiazapines whose metabolisms are not interfered with. One.

DR. TEMPLE: Actually, a lot of that, if they get down to it, they can do a lot of that in vitro. These methods are available. Actually, our labs can help them. We like interesting projects.

DR. FRANK: I guess my concern has to do with the fact that physicians will know not to prescribe these two compounds together, but will patients know not to take these two compounds together.

In my experience, depressed patients have a lot of stuff hanging around in their medicine chests that they take when they are agitated or anxious, just the kinds of things that we would be concerned about here.

So, physicians may read labels, but patients don't always. I am not sure what the potential is for this in terms of real adverse experiences.

DR. TEMPLE: We are not either, but there are things you can do. They are probably

unwelcome, but let's mention what they are.

As you know, triazolam labeling, itself, includes a patient package insert and the drug is marketed only with unit of use packaging, so that patients can read all of the many words that we decided and the company decided they should see before they get it.

One can certainly consider a patient packet insert for this drug, if one thought that interaction was so important as to do that. We don't have too many patient inserts. I don't think any other antidepressants have them.

But if that is considered important enough, we can certainly -- you can propose it and I imagine the sponsors are likely to accept that.

DR. FRANK: I think that sort of comes back to Dr. Charney's question, which is what are the behavioral consequences of this four-fold increase.

DR. LAUGHREN: We do have the pharmacokinetic data, if you want to present it.

DR. LIN: The four-fold increase of the triazolam is very dangerous. I think a lot of people could get very very confused with that.

DR. TAMMINGA: This is not the only drug

that we use in our daily practice that has drug/drug interactions. I don't think it would be fair to exclude this drug simply because there are interactions that people can learn about and know about.

DR. TEMPLE: That is fair. And for example, the question of what erythromycin does to triazolam blood levels is not, to my knowledge, worked out yet. And there are plenty of those sitting around waiting to be discovered.

DR. LEBER: I wanted to raise another point, too. The assumption that, by lengthening the time of elimination for triazolam, that you actually make it a more dangerous drug is unproven.

Part of the risks of rapid elimination of a drug like triazolam may be related to the speed of elimination between nightly doses.

For all you know, you are in a sense dalmanizing, if you want to use the word, this drug and who knows what consequences that has. You might have to adjust the dose. But those things are still not certain yet.

DR. TAMMINGA: Could we just see your overhead a minute. This is the overhead that would suggest what you found.

MS. SAHAJWALLA: This is data taken at half an hour post dosing, one-and-a-half hours, 2.54 and 9 hours. And this is for triazolam group. And this is for when nefazodone and triazolam were co-administered.

So, if you look at the concentrations, it increases -- concentrations at half an hour increased from 1.75 to 2.52. DSSG percent change when triazolam was administered alone was -5.74 versus 7.21.

If you look further down at one-and-a-half hours, it decreased from 31 to -17, and at two-and-a-half hours it decreased from 17.8 to 66.

Similarly, at four and nine hours, it decreased from seven to 63 percent.

And CPT changes were also significant. They increased from -1.4 -- a range of 1.4 to 10 to a range of 8 to 65. Similarly, HEYE percent changes were also significant, and sedation scores were also quite significant.

DR. TAMMINGA: Could you identify what those initials stand for, DSST, CPT, NEYE.

DR. SAHAJWALLA: This is digit substitution and I think hand and eye coordination, and that is the sedation score.

DR. TAMMINGA: So, these are the behavioral data that Dr. Charney just asked for.

DR. SAHAJWALLA: These are the concentration profiles.

DR. TEMPLE: There is an effect both on half life and C Max. 3A4 is importantly found in the gut and is responsible for a fair amount of first pass effect. So, that might account for why, with a single dose, C Max is elevated. And then it looks as if the half life is greatly increased also.

DR. SAHAJWALLA: Yes, half life increased from, I think, two hours to almost twelve hours.

DR. TEMPLE: So, it basically changes the whole nature of the drug. At some dose this may be just what you want, but somebody would have to figure out what the right dose is.

DR. TAMMINGA: These kind of data would be featured in the labeling so that physicians would not presumably prescribe this without knowing necessarily the specific data.

DR. TEMPLE: At this point there would be some sort of specific don't-use-it-together statement, whether that would be in warnings, precautions or where. You know, we are listening.

You obviously feel that it should be quite prominent. So, we could put it in dark print or we could even box it.

DR. HEZEL: I would want it to be part of a patient information insert. I mean, in response to the comments that patients have things hanging around in their medicine cabinets and may not be able to be informed, to withhold this kind of information would actually be interfering with the patient is consenting to be treated, knowing of these consequences, preventing informed consent.

DR. TEMPLE: Is that the sense of the committee, that we should work toward a patient insert on this.

DR. CASPER: Yes, I think it would be very important, because even if the physician says, don't use benzodiazapines or don't use that and valium, the patient, first of all, doesn't remember the trade name. They need a list that gives them the trade names and the generic lists at home. So, I think this would be very important for them to take.

DR. HAMER: To some extent, though, I think we are getting into what you almost might think of as an order effect in terms of order in

which these drugs came along.

In other words, there is clearly, for example, an interaction with triazolam. But I am not quite sure which it is that we are saying is unsafe, in a sense. I mean, maybe I am not phrasing it right, but it has been maybe unsafe to add triazolam to this medication. But do you put that warning in the triazolam labeling or here.

And the answer is going to be clearly here, because triazolam is out there, it has been out there, all those sorts of considerations. But the problem in terms of safety, in the absence of the other drugs, is not with this drug. It is with the interaction with all the other drugs.

And I mean, I would hope that to some extent, that the FDA would know how to address that in labeling. They have had to address those issues before.

DR. TAMMINGA: That would be a point that I would wonder, whether or not something like this would actually need a patient insert. This isn't the first drug at all that has had drug/drug interaction. And what have been the most effective ways to avoid bad side effects with drug/drug interactions that the FDA has found in the past.

Because of the lack of patient inserts with drugs, people who prescribe drugs and people who take drugs have figured out effective ways to avoid serious drug/drug interactions.

DR. TEMPLE: We hear a high level of concern and actually we didn't write a patient insert, I don't think, for tephenadine, where we were very worried and tried to communicate in other ways.

But I think we need to think about whether or not this is appropriate here. And we certainly would do that and I hear at least some sentiment for it.

Now, you may want to make a still stronger statement, but we certainly would think about that possibility.

DR. HEZEL: With the continued development of new drugs and newly-discovered drug/drug interactions, is it not possible, then, to go back to existing drugs and start incorporating that information in labels.

I mean, it is not a static database. I would think that all labels would need to start evolving to reflect that in order to reflect patient safety.

DR. TEMPLE: Well, we are, in fact. We are proposing revision of labeling of tricyclics now to reflect their interaction with drugs like quinidine and phloroxidine and peroxidine.

It is very daunting. The more you look, the more you discover and the limits of what we are going to discover are not nearly over. Grapefruit juice, corn, and all sorts of other inhibitors are all around us.

And it is a challenge, not just for us, but for the whole community, to try to list these things and keep a count of them. I don't think we have them figured out yet.

DR. HEZEL: No, but just because it is difficult doesn't mean we don't start addressing it. I mean, it is going to get more complex, the more information we have.

DR. TEMPLE: We are relabeling the tricyclics to reflect that. People are studying the impact of grapefruit juice on a variety of substances, like the hydroperadine, calcium channel blockers. And there are mountains of information coming. And it will get into labeling as we discover it, for sure.

DR. TEMPLE: It seems that consumers

need to start rethinking that there is a pill for every ill and they are all safe. That is sort of something that we are evolving out of and starting to understand that things are more complicated than we once thought.

DR. TAMMINGA: That would be a superb message.

DR. HEZEL: We have to start the message in regulation.

DR. TAMMINGA: We can all have our own opinion on how the patient consumer ought to get reported about drug effect. But I would certainly agree that the idea that there is a pill for every ailment without side effects is a message that needs to get across.

In fact, I bet that is why problems with drugs come up to a large degree, because of undue expectations and incorrect use, based on those expectations.

DR. HEZEL: It is my opinion that consumers believe once drugs have been approved, though, that they are safe no matter what, because there is this agency taking care of them and looking after all that.

So, I think we have to help them

understand the complexities of it and what that really entails.

DR. TAMMINGA: But if we try to protect the public to too much of a degree, we start to cooperate with that fantasy rather than inform the fantasy.

DR. TEMPLE: There really is a new appreciation, both here and everywhere, about the potential for drug interactions, because there have been some very striking experiences. Tephenodine is one but there are others.

And that is a growth area that we are going to discover large numbers are involving large numbers of drugs. We are all going to have to come to grips with that, including patients that go to several different physicians for medication.

Even the best will in the world, they are not going to discover all of them. I don't know if people should start carrying lists of the things they are on or whether central pharmacy arrangements will do it, but there is a lot of work here.

DR. LIN: I want to reiterate the suggestion that more drug interaction studies should be done with this drug.

I think in terms of the benzodiazapines,

it looks like the pattern is that the benzodiazapines are metabolized by the P450 isozymes, interacting with drug.

Loazapam, which is not metabolized by the P450 enzymes, does not interact with the drug. And it would be a good idea to do more drugs to see if the pattern holds.

Also, antidepressants are very often used in combination with neuroleptics and probably it would be a good idea also to test other neuroleptics that may be used with this drug in combination.

DR. TAMMINGA: I wonder if the committee has any more comments to make on safety or concerns to express or whether it is time to draw our opinion and vote on safety.

Has the sponsor provided evidence that nefazodone is safe in the treatment of depression. Will all those who say yes raise their hands.

DR. HAMER: Can I raise my hand with a qualification, and the qualification is assuming that the FDA writes appropriate labeling to handle interactions.

DR. TAMMINGA: I guess I was voting based on that assumption.

DR. SCHOOLER: Including a re-do of what the five percent figure is.

DR. TAMMINGA: Was that unanimous or were there any abstentions or negatives.

DR. FYER: I think it was unanimous, given Dr. Hamer's comment.

DR. BERNSTEIN: The vote was unanimous.

DR. SCHOOLER: I just have to come back to this. Did the comment that I made regarding, what is the five percent figure for significantly different from placebo, that it be dose dependent. Is that also in the discussion of safety.

DR. TEMPLE: There is a table in the review that shows what -- actually fairly striking dose, considering how crude the dosing is -- fairly striking dose response relationships for a number of the adverse reactions where you might expect it. And we often put a table like that in the labeling.

DR. LAUGHREN: And we are planning to do that here. We will address dose response for adverse events.

DR. TAMMINGA: Now, I would like to draw this part of the meeting to a close, our discussion of nefazodone. We will break for lunch for an hour.

MR. BERNSTEIN: We will be back at 3:00 o'clock to discuss risperdal.

(Whereupon, at 1:56 p.m., the meeting was recessed, to reconvene at 3:00 p.m., that same day.)

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A F T E R N O O N S E S S I O N

(3:03 p.m.)

DR. TAMMINGA: This afternoon, we will switch topics, and we will discuss some preclinical toxicity data relative to the risk benefit assessment of risperidone. And this is a new drug application that we considered at out last meeting, 20-272, from Janssen Research Foundation.

Dr. Laughren introduced those issues this morning and first we will have an FDA presentation and then some sponsor's presentation or response, before discussion among the committee.

And Dr. Glenna Fitzgerald will present the information from the FDA.

Agenda Item: FDA Presentation.

DR. FITZGERALD: Thank you, Dr. Tamminga, and committee members. This is going to be a very brief presentation, so you can be thankful that it will not be a delayed afternoon.

As Dr. Tamminga just mentioned, at the April 29, 1993 meeting of the psychopharm drugs advisory committee, the data for the use of risperidone for the management of manifestations of psychotic orders were presented.

Your vote was unanimous that evidence

for both safety and efficacy had been provided.

Since that meeting, we have become aware of somewhat unusual findings in rodent carcinogenicity bioassays, which we wanted you to be aware of.

A summary of these findings is also included in your package for this meeting, which I am sure you have seen, and there also are copies of my overheads separate from that.

As a consequence of its activity as a B2 receptor antagonist, risperidone administration results in significant elevations of prolactin levels in both rodents and humans.

Drugs with this mechanism of action are commonly associated with an increase in endocrine tumors in the rodent carcinogenicity bioassays, specifically mammary gland tumors, pituitary, and endocrine pancreatic tumors.

The specific question of the relevance of rodent models for assessing potential human risk from antipsychotic drugs, which are associated with elevated levels of prolactin, was addressed in a May 1977 meeting of the FDA toxicology advisory committee.

The committee had a consensus, and I am

going to quote directly from those proceedings, with respect to what they concluded.

First, with regard to carcinogenic potential to the pancreatic islets, no conclusions as to relevance for human risk can be drawn until further pharmacological or physiological data are available which would demonstrate whether or not there is an action of prolactin on the endocrine pancreas.

At that time, there was no evidence -- this is not in the proceedings but I am just saying, at that time, we had no evidence for any kind of prolactin role in the pancreas. There has, since that time, been some minimal evidence that prolactin receptors may exist in the pancreas.

Point number two. With regard to the occurrence of mammary tumors, it was the consensus of the committee that, first, prolactin inducing compounds are all considered to have carcinogenic potential for the mammary glands in rats and mice.

Second, there is known to be a general correlation between the duration and extent of increase in plasma prolactin levels and the degree of mammary carcinogenicity in rodents.

And third, there are major differences

in the hormonal and reproductive physiology between rodents and humans, including some related to the role of prolactin.

At present, the committee feels there is insufficient evidence to extrapolate with mice and rats to humans with respect to the role of prolactin in human mammary carcinogenesis.

It is therefore the opinion of the advisory committee that the rodent studies are not relevant to a determination of the magnitude of the potential for human risk from mammary cancer.

That ends the conclusions from that committee meeting, and these conclusions have provided the basis for our regulatory decision making with respect to drugs which elevate prolactin levels in rodents, and humans as well, and which are associated with an increase in endocrine tumors in rodents from 1977 until the present time.

When we first looked at the mouse and rat carcinogenicity studies for risperidone, it appeared that the findings were not substantially different from those observed with other marketed antipsychotic drugs for which we have data, and I must say we have rather minimal data for the drugs on the market.

The first overhead is a summary of tumor types seen with risperidone, haloperidol, chlorpromazine and pimizide.

It also contains data for drug A, which is not identified, a drug not marketed in the United States because of the overall tumor pattern, and for drug B, which was not marketed because of the finding of pancreatic tumors for that drug.

And at that time, when it was being considered, it was thought that risk could not be assessed because of the inadequate information about prolactin effects in islet cells.

It also should be noted that clozapine is not on this slide. We do have data for that drug, and there are no increases in rodent tumors associated with clozapine administration.

Also, you will note that chlorpromazine also has an increase in pancreatic tumors. And the reason that there was no issue with it is that the bioassay was done several years after it had been on the market. In fact, the results that we have on chlorpromazine are maybe about 10 years old, at most.

The next slides summarize the data for the risperidone carcinogenicity studies.

On the left, are mammary gland, lung and pituitary gland. And you will notice that, in female mice -- this is the 18 month carcinogenicity study in mice for risperidone -- in female mice, mammary gland adenocarcinomas were statistically significantly increased across dose groups and also pituitary adenomas, benign tumors, were increased at middle and high dose.

There is no slide for male mice because there were no tumor findings in male mice, although perhaps the dose used in that segment of the study may have been a little less than optimal.

The next two slides will summarize the findings in the rat carcinogenicity studies. This is the two-year rat carcinogenicity study for risperidone, and this slide shows only the female segment of that study.

It shows that mammary gland adenocarcinomas, again, were also significantly increased in female rats treated with risperidone, with no increase in benign mammary tumors, which occurred both in control groups and in dosed groups.

The next slide summarizes the findings in male rats, and it shows a significant increase, both in benign tumors of the endocrine, pancreas, as

well as in mammary gland adenocarcinomas.

It was this finding of a significant increase in mammary gland adenocarcinomas in male rats that caused us particular concern.

We therefore undertook to compile the available data from carcinogenicity studies for the marketed drugs which I have mentioned previously in this class, the drugs for which we have data, as well as the two that are not marketed in this country.

The next two slides will summarize the data for mammary gland neoplasms, which occurred in all of the studies which were available to us, or at least all of the data that we could find.

This slide summarizes the findings in female mice. There was no increase in mammary tumors associated with clozapine administration. Risperidine, haloperidol, pimizide and drug B all caused a dose related increase in malignant mammary tumors.

There is no slide, again, for male mice, because there were no significant findings for any of these drugs in male mice.

The next slide summarizes the findings in rats, both males and females. As I said earlier,

there was a significant increase in malignant mammary tumors in both male and female rats treated with risperidone.

The two unmarketed drugs caused malignant tumors in female rats but not in male rats. Neither benign nor malignant mammary tumors were observed in rats of either sex treated with clozapine, chlorpromazine or haloperidol.

It should be noted, however, that one cannot put a lot of reliance into the haloperidol study because there was an incredibly high mortality associated with that study and it is conceivable that the animals didn't live long enough to develop tumors.

Because the findings of mammary gland malignancies in male rats treated with risperidone appeared to be unique in our experience, we decided to present the data to the CDER carcinogenicity assessment committee, so that they could evaluate what they thought the relevance was to human risk.

In conducting their deliberations, the CAC considered the following points. The profile of tumor findings in female rat and mouse overlapped with the profiles observed for other antipsychotics, as I showed you on the first slide of the pattern of

tumors. But it was not identical with any one particular antipsychotic drug.

The tumors identified have been associated with hormonally responsive sites in rodents.

Point number two, the finding of increased mammary gland animal carcinomas in male rats was unique among investigative antipsychotic drugs.

Although prolactin levels were not measured in the risperidone carcinogenicity studies, there are data from a six week study with risperidone in rats in which prolactin levels were elevated, both in males and females. The elevations were higher in females than in males.

It is not known, we don't have the information, at least, about how these elevations compare with the magnitude of elevations which were seen with the other antipsychotic drugs for which the carcinogenicity studies were done.

It is very difficult to compare prolactin levels across studies, because they are very difficult to measure accurately, they are dependent upon endocrine status, time of day, and many other factors.

Point number three that they considered, there is presently no epidemiological data indicating increased risk for breast cancer for humans using antipsychotic drugs. However, these data are limited.

Prolactin levels are elevated in humans, as in rodents, following treatment with these agents.

After deliberating on these points, the questions that the committee was asked to vote on are shown in the next three slides, together with their vote.

The first question presented to the committee, is there a significant difference in the findings with risperidone compared to marketed antipsychotic drugs because of the mammary adenocarcinomas in male rats.

The vote of the committee was, yes, they thought there was a difference, and no five people. Eight people voted yes and five people voted no, they did not think there was a substantial difference between risperidone and other drugs.

The second question the committee was asked was, even though the pattern is different, do you believe that the relevance to humans is unknown.

And the committee voted unanimously, yes, they believed that the relevance to humans is, at this point in time, unknown.

The third question and the final question the committee was asked was, can the additional concern be adequately addressed in labeling by stating the findings and stating the unknown relevance for human risk. And again, the committee voted yes, unanimously, that the concern could be handled in labeling.

That is all I have to say and I would be happy to entertain questions.

DR. TAMMINGA: I have one question. Can you tell us who this committee is.

DR. FITZGERALD: The carcinogenicity assessment committee was established in the center for drugs about two or three years ago, perhaps. It is composed of the supervisory pharmacologist. Dr. Temple is usually a member. We also have, for this particular committee, we had a member from NTP -- National Toxicology Program at Research Triangle Park -- and we had also two experts from National Center for Toxicological Research, people who were knowledgeable, both about rodent bioassays, tumors, and in particular, endocrine effects.

It also includes the statistical people who have been involved with these drug products, as well as from time to time, different experts as deemed necessary.

DR. TAMMINGA: Questions for Dr. Fitzgerald.

DR. CHARNEY: I am aware of a study that may have been published about a decade ago, that looked at whether or not there was an increased incidence of breast cancer in patients on neuroleptics. And I think it was a negative study. But is there more recent documents.

DR. FITZGERALD: There are very little data available to us. And I am not an epidemiologist. I think I will defer to Dr. Laughren on any questions of human epidemiology.

DR. LAUGHREN: We haven't reviewed the epidemiologic data in anticipation of this issue being brought up. I think the company is planning to address some of the more recent epidemiologic data, if you can hold off on that.

DR. LEBER: I believe -- and this is by remote memory -- that the issue of risperidone's role in this was covered many many years ago by the agency officially.

DR. FITZGERALD: By that committee.

DR. LEBER: By that committee, and I believe in about 1978 or so, there was some discussion of neuroleptics in general and whether they were a risk factor for the induction of mammary tumors.

I think the conclusion was that it was not. However, there was the issue of tumors bearing receptors for prolactin and there was concern that they might promote the growth of already established. But that is probably dated by about what, some 14 years or so.

DR. FITZGERALD: Yes. I don't think there is any better information available, though.

DR. TAMMINGA: Additional questions for Dr. Fitzgerald.

Thank you. We will move on to the sponsor's presentation. This is Dr. Bruce Givens.

Agenda Item: Sponsor's Presentation - Janssen Pharmaceutical.

DR. GIVEN: Good afternoon, I am Dr. Bruce Given, senior vice president and head of U.S. research and development for Janssen Pharmaceutical.

I am happy to report that, in this particular case, the company is in full agreement

with the FDA division and with the carcinogenicity assessment committee concerning the final conclusions regarding the risperidone carcinogenicity findings and risk.

We also are in full agreement with the recommendation of how this should be handled in labeling.

For that reason, we have elected not to make a full, formal presentation, and save the committee and the public an hour of slides, some of which would be repetitive, relative to what you have just heard.

I should say, however, that there are subtleties in how we got to that same conclusion, and it is possible that those may come out during the discussion.

We have actually spoken with the chairperson and with the executive secretary of the committee beforehand, and there is agreement that if, during the discussion, we have information that could be of use to the committee or to the public, in helping deal with, perhaps, speculation, that we could step forward and be recognized. We have prepared quite a bit in that regard.

Just to let the committee know, we have

brought some consultants with us who may be of some use to you. Dr. Charles Capen is professor and chairman of veterinary pathobiology at Ohio State. And Dr. Terry Nett is professor of reproductive physiology at the Department of Physiology, Colorado State University.

Both are experts in the relationship between prolactin and rodent neoplasia and carcinogenesis. And you should feel free to call on them at any time if you would like.

In addition, we have two clinical consultants -- Dr. William Crowley is professor of medicine, Harvard Medical School. He is at the Mass General. Dr. Crowley is a former member of the endocrine advisory committee and is a well known expert in prolactin physiology in humans.

In addition, we have -- and this is specifically, I think, of value, perhaps, Dr. Samuel Shapiro, director of the Sloane epidemiology unit, research professor of epidemiology at Boston University School of Medicine.

Dr. Shapiro has had at least a 20-year interest in the relationship between prolactin and human breast cancer, and in fact, does have a complete review of the epidemiology literature, if

you would choose to call on him.

I should point out that, not to presage what he would say, but it is true that there is not an overwhelming amount of data in neuroleptics, per se, with respect to breast cancer risk.

However, there has been and continues to be, ongoing epidemiological work, looking at the general issue of the relationship of prolactin with breast cancer risk, either in the de novo state, or in response to drug therapy.

I think that you might find Dr. Shapiro helpful, if this is an issue that the committee would like to hear more about.

So, with that, I am going to step down from the podium. We are here to provide any information that might be of value. Thank you.

DR. TAMMINGA: Well, since the question has already been raised, I would ask the question of either Dr. Crowley or Dr. Shapiro, in your expert opinion, what is the relationship between prolactin causing mammary tumors in rats with prolactin causing cancer in human patients.

I think the data seem reasonably clear. We all know that risperidone increases prolactin in humans and we can see the animal data are fairly

simple, I take it, and there is extensive agreement, what the implications are.

DR. SHAPIRO: Thank you. I think this is one circumstance where the epidemiological data enable us not simply to say that there was no evidence that high prolactin levels increase the risk of breast cancer, but there is evidence to suggest that high prolactin levels do not increase the risk of breast cancer.

The data come from two sources. The first concerns the famous or the infamous reserpine controversy. This is my formal slide.

There have been some studies which have looked directly at the risk of breast cancer in relation to prolactin levels. The first one was a study carried out on the Island of Guernsey in which patients had their blood tested at entry.

And they were divided into quintiles of prolactin and they were divided into post-menopausal and pre-menopausal women.

The numbers of post-menopausal women were quite small in each of the quintiles except one. The numbers were in the single digits. The relative risk estimate was set at 1.0 with the lowest quintile. And the highest quintile was 1.6,

but there was no trend according to quintile and this finding, purportedly, had been due to chance.

Among premenopausal women where they had larger numbers, there were cases in at least two digits of the strata of the relative risk levels. And the lowest quintile was 1.0. And the top-most quintile was 1.0. In the intermediate quintiles it was not significantly different from 1.0 and there was no evidence of increase.

The investigators concluded that the evidence suggested that prolactin does not increase the risk of breast cancer.

DR. TAMMINGA: Could you make sure we know what prolactin levels these quintiles are. Could you at least tell us the range from one to five.

DR. SHAPIRO: Unfortunately, the paper did not give the quintile levels, did not give the actual levels in the paper, but they divided them into quintiles.

DR. TAMMINGA: Say, the fifth quintile. What range would those be.

DR. SHAPIRO: I don't know the answer to that question, I am sorry.

DR. CASPER: Do we know when these

levels were drawn. Is there some variation.

DR. SHAPIRO: Yes, they were drawn at recruitment.

DR. CASPER: At recruitment, but during different times of the day.

DR. SHAPIRO: Yes, different times of the day, different parts of the menstrual cycle, different underlying stimuli, different anxieties, not taking into account the pulses that occurred in prolactin levels. And this is one of the shortfalls of the study. I will come to that in a moment.

But if one looks at the means -- and I think it is important to compare the lowest and the highest quintile, there was no significant difference.

Now, this was a study done in New York among women who reported to a breast cancer screening clinic. At the time that they reported, they had a blood sample drawn and the blood sample was stored at -80 degrees Centigrade. And the patients were then followed for the occurrence of breast cancer.

Eventually, more than six months after the women were found not to have breast cancer -- six months to nine years -- 78 women developed

breast cancer. They were matched with controls, with 135 controls, who did not have breast cancer, whose blood was drawn at the same time, and who were the same age as the women.

The data were then divided into quartiles of prolactin and in a moment I will show you the mean doses.

But if you compare the uppermost quartile with the lowest quartile adjusted simply for age, the relative risk in the uppermost quartile was 1 as compared with 1 in the lowest quartile.

There was a jump to 2.0 in that intermediate quartile. When this was adjusted, in addition, for estradiol, this was blood estradiol level, and this was done because estradiol was found to be significantly associated with breast cancer risk in this study.

The relative risk was 3.3 and significant, but there was no dose response effect as one went up to the third and fourth quartiles. The relative risks were not significant.

Prolactin, it was not normally distributed. There is a tail on the one side. And so, they estimated geometric means. The geometric mean prolactin level in the cases was 6 nanograms

per milliliter, and in the control, 6.06, and of course, this is a non-significant result.

The standard deviations are quite narrow and suggest that there was no difference.

Now, one of the problems you have already alluded to, and that is that there were pulses that, measuring prolactin at different phases of the menstrual cycle presents problems, that it matters whether you measure it during the day or the night.

And it is conceivable, despite these rather reassuring data, that an association could have been missed because of a lack of specificity and a lack of standardization in the measurement of prolactin levels.

For that reason, it is more interesting to measure drugs which chronically stimulate prolactin levels, as perhaps another model of getting at the issue. And reserpine, in that respect is quite helpful.

Now, this is data from the original study that first stimulated the reserpine hypothesis, which was published in 1974. I am embarrassed to inform you that I was one of the co-authors of this study.

We had 150 cases, of whom 11 had taken rauwolfia in the three months before admission. We had two control groups of 600 each. In each of those control groups, 13 had taken rauwolfia. The relative risk was 3.5 and the P value for that relative risk was 0.07.

This next slide, I am not embarrassed to inform you that I was also a co-author. It is a slide in which we did penance for what we had done in the first study. The first study was justly, I think, severely criticized for poor design, for imprecision in the way the data were collected, for failure to report confounding variables, for provoking a cascade of some 20 or more additional studies after the first one, the better conducted of which were all resoundingly negative.

And in these data, we collected data from the same catchment population, the same type of women, using essentially the same method, but with much greater attention to detail and with much greater attention to confounding.

We had 1,881 cases as opposed to 150 in the initial study, and 1,523 controls as opposed to 600 in the initial study. The prevalence of rauwolfia used was 2 percent in the cases and 2

percent in the controls.

These data are extremely stable. They are based on 31 and 34 exposures, respectively, were adjusted by multiple logistic regression for a large number of confounding variables. The relative risk was 0.9, and one could rule out more than a 40 percent increase in the risk.

If one looks at past exposure, which was an attempt to get at whether there was, perhaps, some sort of genotoxic effect, the relative risk estimate that was discontinued at least a year previously, the relative risk estimate was .5 and went down to .9. And if one looked at any exposure, the upper band was 1.1.

Incidentally, we did not claim, and do not claim, that high prolactin levels stimulated by reserpine reduces the risk of breast cancer, if one then continues it. I think this is a fluke finding and simply an illustration that even with large numbers one can get statistically weird results.

Shapiro's second law is that if you don't find some funny results in your set of data, you should wonder about whether your data are correct.

In the same study, this analyzed another

drug that stimulates prolactin secretion. This is an antihypertensive, methyldopa. The relative risk for that drug was 1.0. When one analyzed the duration of use, the timing of use, all of the relative risks were close to, and comparable with 1.0.

Now, there are other ways in which one can try to approach the question of whether drug induced stimulation of prolactin increases the risk of breast cancer.

There have been follow up studies of psychiatric patients in which there has been no comparison group, but the expected rates of breast cancer have been derived from national statistics or from registry statistics.

These studies have limited statistical power, and they were open to other criticisms. But for what they were worth, they, too, illustrated no increase in the risk.

One might also turn to case reports. Prolactinoma is a relatively common lesion. It is one of the more common of the pituitary tumors. And if it increases the risk of breast cancer, one would expect to see a large number of case reports. In fact, there have been very few.

Even the few that have been reported are very likely biased because, obviously, a case of breast cancer that occurs in the absence of the prolactin level would not be reported. And there are, of course, no denominator data.

Then finally, what I should mention is that there is a vast array of what have been labeled case controlled studies, but which really are cross sectional studies in which prolactin levels have been measured after women have developed breast cancer, usually after they have undergone surgery as well, and usually after they have been subjected to chemotherapy.

Surgery, chemotherapy, psychological stress, as you know, all affect prolactin levels. And for those reasons, the findings from those studies aren't interpretable.

My own judgment is that, taken in conjunction, there is now a large body of epidemiological evidence that suggests that prolactin secretion does not affect the risk of breast cancer in humans.

DR. TAMMINGA: Thank you. Questions.

DR. LEBER: I have one. Is there any association between the rate of growth or lethality

of established breast cancer and prolactin level.

DR. SHAPIRO: There have been a large number of studies which are highly contradictory. I would say well over 50 published studies that I have read through. Most of them were very poorly designed, I thought, and incapable of answering the question.

I should mention that, conceptually, when the indication for examining an exposure is confounded with the disease itself, you generally de-randomized the controlled trial to settle it.

Now, we can't randomize prolactin levels. But we also cannot say whether the prolactin does anything to the growth of the breast cancer. It might be the other way around. It might be the breast cancer that stimulates the prolactin levels.

DR. CASPER: You have shown us, now, prolactin levels in physiological amounts, and then the physiological range is not associated with breast cancer. And I have two questions.

The exposure to methyldopa or to rauwolfia, probably for hypertension in those studies.

DR. SHAPIRO: Yes.

DR. CASPER: Was probably temporary and not long-term, is my hung.

DR. SHAPIRO: Oh, no, long term in both instances.

DR. CASPER: Were prolactin levels measured in these patients. Do you have any idea of the levels.

DR. SHAPIRO: No, they were not measured in these studies but it is my understanding -- one can correct me if I am wrong -- that reserpine and methyldopa stimulate prolactin and stimulate it for a prolonged period.

After a matter of years, the prolactin levels begins to decline, but it does not return to normal levels and it remains elevated for as long as you continue to take the drugs.

I would stress that we analyzed our data concerning reserpine and methyldopa for long regular durations of use, and we found no effects.

DR. CASPER: It was well over a year.

DR. SHAPIRO: Oh, well over a year.

DR. CASPER: Because one of the concerns, of course, with the antipsychotics, is that most patients, once they have taken an antipsychotic drug, they take it for years.

And the other issue is, how strongly dopamine agonist, well, reserpine is obviously a very strong dopamine agonist so you would have probably comparable levels. But, depending upon the dose, there is also a certain dose response relationship to prolactin levels.

And I think what is really bothersome is the lack of data on psychiatric patients.

DR. SHAPIRO: I can't answer the question about psychiatric patients. I can't answer the question about dose response. But I can answer the question about duration of use. And this was exceedingly prolonged. Reserpine is among the more potent prolactin stimulators.

It is to be hoped that hypertensive patients take their reserpine, if that is what they are on, regularly and for many years. So, in that sense, the analogy with psychiatric drugs is quite close.

DR. CASPER: We also know that breast cancer actually has a familial tendency. Do you have any data, based on the breakdown by family.

DR. SHAPIRO: Positive family history, it doubles the risk. If it is breast cancer that occurs premenopausal and the family history is in

the mother or the sister, it can be substantially increased.

We actually examined reserpine use and methyldopa use among cases and controls with a history of breast cancer in the family and without, and there was no elevation of the risk in either of those strata.

DR. TAMMINGA: If the committee has no more questions, thank you very much.

I may not be entirely clear what we are supposed to do with these data, Dr. Laughren. Perhaps if there are some specific opinions that you would like us to --

DR. LAUGHREN: Let me try to explain how it is that we are coming to the committee with this now.

Had we appreciated the difference in the tumor pattern between risperidone and other marketed antipsychotics in the country, at the time of our April advisory committee, we probably would have brought it to you as a point of information then.

We didn't, and in the interim, between the time that we discovered the finding and it went to our carcinogenicity assessment committee, we rescheduled it for this meeting.

Subsequent to that, it has gone to our CAC committee. They have given us a recommendation which we are inclined to accept. But bringing it to you now is really a point of information to tell you what our plan is, and really as a matter of full disclosure to you. I am not asking you for any particular vote.

If you wish to discuss it or vote on it, you certainly may, but we are not asking for any particular vote.

DR. HEZEL: What is your plan.

DR. LAUGHREN: Well, the CAC committee recommended that we mention the findings in the labeling, along with the usual statements saying that the relevance for human tumors is unknown.

That is the way they are handled for other drugs that elevate prolactin, and that is our plan for this drug.

DR. HEZEL: What will you do for patient information, in terms of informing patients of that risk, or the suggestion of that risk, in labeling.

DR. LAUGHREN: There wasn't any plan to do anything differently for this drug than is done for other drugs that elevate prolactin.

DR. FYER: There was some discussion at

the last meeting when this drug was considered in full, about putting some more emphasis on the fact that it did have this effect on prolactin, and that since there is such widespread risk for breast cancer in our particular population, that people ought to be allowed to make their own decision about it.

I wonder, hearing some of this data, and Dr. Frank's comment, it is definitely the case that there seems to be no positive evidence. But it is also the case that the data presented have an enormous number of loopholes.

It is also the case that there is a lot of new knowledge about breast cancer and risk, et cetera. I think it is an area in which there should be a fair amount of information provided for consumers so that people can make informed decisions.

DR. LAUGHREN: Is your concern about risperidone in particular or all drugs that elevate prolactin. Are you suggesting that we revisit the entire class of drugs.

DR. FYER: I think that might be a nice idea. But the fact is, this is something that we can do something about because you are about to do

the labeling in this drugs. So, it is someplace where you can make an intervention and perhaps the inference, just by example, will lead people to more informed decisions about other things.

I mean, I think the issue that the levels of prolactin are not really clear in this data, that it is true about the risk, but the data have not been analyzed. I mean, there are all kinds of areas of ignorance here where you can't really say we know for sure there is no increased risk. And people should make their own decisions.

DR. LAUGHREN: It is certainly true that an absence of a finding is not proof of the absence. But again, it seems to me that that applies to all drugs that elevate prolactin. If we are going to do it for risperidone, then we really ought to think about doing it for all drugs that elevate prolactin.

And my question is, is the committee of the sentiment that you think we ought to re-visit the issue for all antipsychotics, all of which, except, perhaps, clozapine, elevate prolactin and other drugs outside of the antipsychotic class that elevate prolactin. Are you unhappy with the current labeling with regard to this issue.

DR. CASPER: I don't know whether I can

answer your question right now, but are we unhappy with the labeling, without the labeling before our eyes, it is hard to tell.

I think there is a prolactin warning in the FDA labeling for all antipsychotic drugs and so, should we revisit the issue, yes, there should be some studies done which would look at the incidence, not of any endocrine tumors, but under psychotics, but just in relation to risperidone.

And furthermore, I think breast cancer in males should also be included, not just in females. Just looking at data in male rats, there might be, actually, an increased incidence of breast cancer in males, but we don't have the studies.

So, we might want to suggest to you, once we have seen the labeling, we might want to visit this again or we might want to suggest some studies. But I had one more concern which your other advisory -- the toxicity or the cancer advisory committee raised.

The pattern of tumors is slightly different and I think you ought to mention that as well. Apparently, there are pancreatic, pituitary and mammary gland tumors. And the committee said the pattern is different from other antipsychotics.

So, that should be mentioned in your labeling.

DR. LAUGHREN: We can certainly consider doing that. The only concern I have about that is that if you look across the other drugs for which we have data, you also see some data.

Do you want us to revisit labeling for the other drugs and talk about the differences. I mean, it gets a little complicated if you are going to try to point out all the differences in these tumorigenicity studies for all the different drugs in the class.

DR. CASPER: I think they should be mentioned. I don't think this is that complicated not to have it mentioned in an insert.

DR. LEBER: I really want to ask another question which is more of a follow up to Dr. Fyer. It is true that in the ideal you would like to communicate fully informed individuals, physicians and patients alike and perhaps those who have a secondary interest in that relationship -- family members, friends, loved ones -- about what the true risks are and what you are supposed to conclude from the evidence.

The problem I have, and this is the practical one, is that if you are going to write

either informed documentation for patients or even for physicians, when you have data of this sort, what is the intent of what you convey, simply to, one, enumerate that you have these facts, you put them down and people can make what they will. Or do you think we have an added responsibility to also interpret them in light of what current judgment among experts is about them.

I mean, what is the purpose of this. Is it to put on record that we know these things happen, because, believe me, every day there will be reports in the literature, in SCIENCE or NATURE or somewhere else about some other phenomena that has been described in relationship to a drug class.

And if all you want to do is inform people, the list will grow and grow. The question is the difference between information and knowledge in these areas, and I would sort of like the committee's guidance on that part of the equation.

DR. TEMPLE One of the reasons that this particular finding has been considered perhaps less important than it might look, is because of an impression -- and we just went through all of this -- that the physiological role of prolactin is different in rodents and humans. So, there is more

than usual skepticism about what these findings mean.

And I guess I would echo what Paul said. I mean, we have a fairly hard time knowing what this means. The best people in the business have grappled with it for decades, and they don't know what it means.

So, what would you be telling a patient if you told them that these tumors are there in a very conspicuous way, like in a patient insert.

It is not that anybody wants to hide it, but when you bring it out and put it in there, why did you pick that. That is my question. That is a real problem.

DR. FRANK: It seems that before you could do the kind of informed labeling that you are talking about, what we really need to know about is, what is the interaction among antipsychotic drug use, family history, and risk for breast cancer in patients with psychotic disorders, because I think they are a special class with respect to health care, stress levels, and a whole host of other things that we know may be risk factors for breast cancer.

So, I think we can't necessarily

extrapolate from general population data and that this is really actually a very complicated question that would require a study that is specific to the issue at hand.

DR. TAMMINGA: I think, though, that at the present time there is no study that is specific to the question.

DR. FRANK: I think that is right.

DR. TAMMINGA: So that, the toxicity data in rats is clear. And then comes the question of what the known elevated prolactin levels in humans have to do with breast cancer.

Although I wasn't necessarily so convinced like you were, Dr. Casper, about the relationship between breast cancer and prolactin levels within physiologic dose ranges, within physiologic prolactin levels, we did then hear some data about drug stimulated prolactin levels, and the relationship between, or the incidence -- the prevalence -- of breast cancer in those situations. Can risperidone in neuroleptics produce similar prolactin levels.

DR. FRANK: But I would argue that hypertension patients are not schizophrenic patients, that they are really different, and

probably different on a host of variables that may be relevant to risk for breast cancer.

DR. TAMMINGA: Then you would have to argue that they were different with respect to breast cancer susceptibility.

DR. FRANK: Yes.

DR. TAMMINGA: On the basis of what kind of data, though.

DR. TEMPLE: How will you do the study. They are all on these drugs. What is the control group. This is not an easy territory.

DR. LEBER: I think what you are grappling with is what we would all like. In any situation where you take a medicine, you want to know what the risks are. In this case, you want to know what the risks of having breast cancer is the result of having taken this and anything else that might be prolactin related.

I mean, if you want to be literal, males or somebody, should worry about pancreas. I don't know if we can get it.

I mean, clearly, each of who chooses the vegetables we eat might want to know their relative etiology for a variety of cancers.

In the here and now, for this drug

product, is there a basis -- now this is the hard question -- for making any unique statement, given what you know. I think I am echoing Tom's point, that there may be class issues here. Perhaps they are unique to being a schizophrenic patient, whatever that means, perhaps not.

But what you are really saying is that we ought to broaden our knowledge in general. But that statement could be divorced from any action on this drug and I guess I would like to know that.

There is a difference between exhorting us to learn more and then making a practical concrete recommendation vis-a-vis this drug.

DR. CHARNEY: I would essentially agree with that, because you could equally say that clozapine is different than other antipsychotics. And that is not really informing the patient or even the practitioner because the meaning of that is not clear.

So, you could have a package insert that says, risperidone is different from other antipsychotics, chlorpromazine is different than other antipsychotics. Essentially, you are saying they are all different from each other, perhaps on this variable, and the end result is information that is not informative in terms of drug use.

So, I think it is a little premature other than to note that more work is needed in this area.

DR. CASPER: But I think we have raw material from Janssen, actually some evidence that the population, namely schizophrenic patients, might be different.

I think you argued that actually the rats, which you tested now in the 1990s or the late 1980s, were different from the rats which were tested in the 1970s because they are a different breed.

What you argued, essentially, was that they are less mobile and that they overfed. And we have exactly this problem with schizophrenic patients. Well, not only with schizophrenic patients.

But if you argue that they might have a higher incidence of tumor because they have other risk factors, there we have an argument that this population, indeed, might be different, and therefore we should be more careful, with at least warning them or if they have a family history of tumors, that the physician might decide not to give high doses.

DR. TAMMINGA: Of course, one could argue that schizophrenics actually have a lower risk of breast cancer because the prolactin suppresses estrogen levels and estrogen surges in women throughout their menstrual cycle and puts them at lower risk.

Once you start carrying on, you can carry on in any different direction. We need to speak to the data, I think, and echo Dr. Charney's conclusion that we certainly need to study it more.

DR. GIVEN: The only thing I would say, we would be willing, if you would like, to put out the class labeling. We do have it.

I think the interesting thing about the class labeling, as we have really had to dive into this issue over the last six to eight weeks, obviously in some detail, is that the class labeling, I think, really is a pretty good piece of writing, because it has not unduly, I think, scared patients and physicians away from treatment with drugs that are really needed.

But on the other hand, the class labeling has also not discouraged ongoing epidemiology work. This epidemiology work is difficult, it is never conclusive. But as you could

see from Dr. Shapiro's presentation, the epidemiology continues to be looked at with these drugs.

And it might be of value to the committee to see that class labeling, if you would like to.

DR. TAMMINGA: Please.

(Slide is shown.)

DR. TAMMINGA: The proposal now is that this same labeling be included as is for risperidone.

DR. TEMPLE: Presumably, the distinguishing features of the results here would be mentioned, would be described. Certainly, one of the issues that was brought up was whether or not the fact that risperidone was different from other drugs should be included.

And again, the problem I see with that is that if you are going to point out the differences for risperidone, for other drugs should we also do it. And it is just a very cumbersome thing to try and do. They all differ in one way or another. And is it an important difference.

Our carcinogenicity committee has already concluded that the relevance to humans is unknown. If that is the general consensus, then why

is it important to point out differences in the pattern among different drugs in the class. I don't quite follow that.

DR. CASPER: There are different ways to present the data or the information. I think you would want to include that in rodents and mice and rats -- male and female -- you have pituitary and pancreatic and many issues.

So, that information you don't need to say necessarily is different.

DR. LAUGHREN: Absolutely, but the plan was to do that, to describe in full the findings for risperidone. The question is whether or not you would go on to say, this pattern differs from chlorpromazine, it differs from haloperidol. That is the question I have, whether or not that adds any value to the labeling to do that, given that we don't know the significance of those differences. We don't know how to interpret them. That is the problem.

DR. TAMMINGA: I have another question of the company pertinent to this. In humans, does risperidone produce a different elevation of prolactin than other neuroleptics. Maybe nobody would know that.

DR. GIVEN: We have that. (Slide is shown.)

Now, let me give some caveats with this slide. First of all, we had a great deal of difficulty finding prolactin levels with historical agents, largely because they tend to date back to the days of prolactin bioassays.

So, we were winding up with an apples and watermelon comparison.

So, what you are looking at here is all radioimmuno assay prolactin levels. Now, let me make a couple of other points.

In the risperidone here, what you have is the dose which you may all recall from April, we feel to be the optimum dose.

At higher doses, a number of things happen. First of all, efficacy seems to be lost to a certain extent. There are greater adverse experiences. And in fact, prolactins continue to go higher.

DR. TAMMINGA: How high.

DR. GIVEN: In females they can reach up to 50, 60.

DR. TAMMINGA: At what dose of risperidone.

DR. GIVEN: Up to 16. But they go higher at 10, they go higher at 12, they go higher at 16. They definitely go higher with higher doses. And there is a lot of noise in this data, too, because we did not put the background levels here. But as you recall, there were not long wash-outs. So, this data is pretty difficult to interpret.

Our only point in wanting to put up this slide was to say that the levels with risperidone fall into that broad category of other drugs. In an individual patient or at a higher dose, they may be somewhat higher. But basically, this is sort of what we were able to put together.

We are not surprised. Reserpine methyldopa came out of the literature. These were not comparative trials. Haloperidol and risperidone were out of the same trial. But again, other risperidone doses produced higher levels than this. So, I don't want to misrepresent this data at all.

DR. TAMMINGA: Perhaps we could see the FDA data that you have, too.

DR. MOSHOLDER: This is Janssen's data from the two clinical studies where prolactin levels were measured. This transparency is study 024. There is no placebo group in this study. There was,

however, a haloperidol 10 milligram group as a control.

And one can see here, at the top, for female patients, female and male prolactin levels are slightly different normal ranges, as shown down there. The baseline values for the means in this column, and then an end point here.

And one sees that there is a dose dependent increase, for the most part, with increasing risperidone dose, and there is a greater magnitude in comparison to the haloperidol 10 milligram change, which is shown down here.

And similarly, this displays the data for the male patients, both the mean baseline prolactin and the mean end point prolactin. And again, somewhat greater magnitude difference from baseline to end point than for the 10 milligram dose.

The sponsor also obtained prolactin levels in study 204 and here, there was both a placebo group and a haloperidol 20 milligram control group, in this case. And one sees at the top here, this is the mean prolactin level data for male and female patients combined.

And again, one sees more or less a dose

dependent increase, although actually slightly less in the 16 milligram group, going from baseline here to on treatment. And for comparison, the change in the haloperidol group.

If one looks at the patients who were normal at baseline prolactin and then there elevated above normal on treatment and take simply the proportions of patients in each dose group, the percentage here is shown down at the bottom and the actual numbers, which we can see roughly 30 patients in each group who had paired prolactin levels from baseline and treatment.

One sees that actually the highest percent is in the 16 milligram risperidone group, although, again, this was an N of only 34.

DR. TAMMINGA: Thank you.

DR. HAMER: At baseline, one would expect them all to be the same except the randomized. There should be no pattern.

DR. MOSHOLDER: Well, that would be the expectation, although one question is, with the wash-out period, I suppose many of these patient may have been on other drugs. But still, you see the baseline for the 16 milligram group is rather higher.

DR. HAMER: I mean, I have seen enough

of these things, not with these particular drugs, but where completely inadequate wash-outs are allowed between treatments and there are all sorts of order effects and sequence effects and time effects and everything else.

DR. TAMMINGA: Even if you don't pay any attention to the baseline and just compare these to known normal ranges, you can take a look at the end point treatment analysis, the mean treatment.

DR. GIVEN: I could maybe make a point that would be of value here. Remember, some of these trials were placebo controlled, and what you see is that the placebo actually does fall. So, there is clearly a time effect here and these patients are not fully washed out by any means.

That is why I say, the baseline makes it hard to interpret but you know, you do get an on-treatment effect which, presumably at the end of an eight-week treatment period, probably represents what your drug is doing and not all that much carry over, I would expect.

DR. LIN: I have a somewhat different question about the mechanism or reason for the differences in the carcinogenetic effect of the medicine between rodents and human beings.

I think Dr. Temple earlier said these effects of prolactin is different between rodent and the human being. If that is the case, then maybe that would be comforting information in terms of suggesting that what happened to rodents may not happen to people. I wonder if people have enough detailed information.

DR. HEZEL: I wanted to comment on Dr. Laughren's question about describing differences in the various drugs in the label and whether or not it was significant.

The thought I had about it was that FDA approval really isn't the end of research. It is more the beginning of a much larger human experiment. And maybe description of those differences would be important in stimulating other epidemiological research and practitioners identifying things that would be helpful, to know whether or not those differences are significant or have meaning for prescription or consumption.

DR. LAUGHREN: Again, the major concern that I have is the practical one of how to describe -- first of all, to present the findings for these tox studies, in itself, is a challenge, to summarize all that data.

To then try and describe the differences between a particular drug and other drugs in the class expands labeling. I appreciate the need for greater research in this area, to try and find out whether or not there is a real effect here. But I am wondering if that is the best way to do it, to put it in that section of labeling.

DR. HEZEL: Well, that is another issue for debate, but if it is in the FDA files or the company files and not accessible to consumers -- the prescribers or the patients -- I mean, it has got to be somewhere. But I don't know where you would want to put it.

DR. TAMMINGA: Many of these data are in the literature already.

DR. LEBER: I was sort of trying to listen with a third ear. I don't mean to over-do it, but are we hearing each other correctly here, because I think it will be in labeling.

The section of labeling that would describe the results of these studies will describe the explicit results. What I believe Dr. Laughren is trying to avoid doing is drawing up a discussion section in which you say, risperdal differs from haloperidol in this way. It differs from compozine

in this way, from thorazine in this way, and so on down the list.

You would end up with a set of explicit, you know, dyadic comparisons which would be boring, not particular informative because, if you were really interested in it for research purposes, you could easily take the labeling in which we describe what the results were -- unfortunately the results would have been gathered across three decades in different studies with different animals with different standards.

I don't know what use you would make of them, but if you were interested and so motivated, you could at least collect it from the raw descriptions.

But I think what he is raising objections to -- and I think I would as well -- is to the idea that we would write a long soliloquy about, this isn't like this and this is like the other and so on. I don't know what it would mean.

DR. TEMPLE: I think if there were thought that this was likely to be meaningful or mattered, we would be taking a different posture.

The best estimates of the people we could assemble -- and I think the outside world

would think the same thing -- was that we don't know if this means anything.

If you write something down as if it means something, but it doesn't, you shape what people use, and this might not be the best basis.

I mean, the particular concern that the tumors show up in the males here might not be a very good basis for making a choice of antipsychotic drugs.

It is unfortunate that we don't know the whole answer, but when you present something, it implies that it is information that is meant to be used, always a difficulty, and it is not always easy for experts to make use of this. It is doubly hard for a lay audience to make much sense out of animal tumorigenicity studies.

The other thing I need to add is that individual person observations are not going to get the answer here. The answer is going to depend upon use that is going to take place over the next very long period of time.

And as a final note of discouragement -- Sid can tell me if I am wrong here -- we can't figure out whether taking estrogens is bad for you yet. There have been hundreds of studies by now.

They go this way, that way, they look at one subset this way, one another.

And the most obvious thing to worry about, we don't have an intelligent answer. So, I don't expect much in the future. Maybe that is more discouraged than I need to be and you can tell me I am all wrong. But it is very hard to work in these areas. There are too many factors that affect it.

DR. TAMMINGA: I would actually like to concur with what you are saying, because it had been my thought, based on all the information here, that saying something too specific in labeling would be misleading, especially after seeing those prolactin data -- the human prolactin data.

We are expecting that this mammary tumor is mediated through human prolactin levels. And when we actually look at the data that you just presented, and that was presented by Janssen, if you actually go out in a state hospital, like many of us have done, and measure prolactin levels in both males and females, these are just nothing like the levels you see. These are rather reasonable and rather low.

Of course, for any antipsychotic, the level of prolactin depends on not only type of drug

but, probably moreso, dose of drug and duration of administration. So that, there are so many factors that make more difference, I would say, than neuroleptic, that I think we get an epistle for the drug labeling by the end of it, which we want a brochure to be used as well as to be correct.

DR. LIN: I wonder if I didn't make myself clear. I was asking to see if the company has additional information about differences between the rodent and human being in response to prolactin.

DR. GIVEN: Yes, Dr. Crowley can give you a brief presentation in that regard. I am not sure I would call it data. It is more a sort of general overview.

DR. CROWLEY: I think that is a very reasonable question because this has to be put into a perspective, because prolactin in the rodent and prolactin in the human are entirely different, number one.

And number two, what Dr. Temple said is actually right on target as well, in that we still don't find that prolactin has as many effects as we think and find in other animal species.

In fact, for example, in the human male there is no known action for prolactin, other than

to get pathologic levels and disruptive.

And to give it some perspective for you in what you are asking, if you look at prolactin, most of us remember two things about prolactin from medical school. One is that it is associated with lactation, in that it causes milk production from the breast, and second, that it is under negative tonic control by the brain. And those are really very close to a lot of what is known in terms of role.

It is under hypothalamic control by both dopomanidric and serotanergic neurons, and that is where you collide with it here on this committee, and that is that you are manipulating the biogenic amine receptors by a series of drugs, as well as, increasingly, the pathonergic neurons.

But the predominant influence from the brain is a negative one via dopamine, such that, if you cut off the hypothalamic pituitary stalk, all other pituitary hormones drop and prolactin levels go off.

The second point that is very very important here and was mentioned by the chairperson, is the interaction between estrogens and prolactin, which is very positive and, in fact, during

pregnancy the prolactin levels increase dramatically to well within the ranges that you are talking about here on the drug, and also with estrogen administration, birth control pills, a variety of things.

In fact, 30 percent of the cells in the pituitary become prolactive during pregnancy and the physiologic blind spot enlarges.

And finally, suckling reflex via spinal affearance(?) causes a very positive influence by relieving the dopamine inhibition and causing prolactin to occur, by as yet unknown mechanisms.

If you then look at the actions of prolactins across the vertebrate animals, you find things that in lower vertebrates, osmoregulation is important. And where we may see this in the human may have something to do with the enormous levels that fetuses are exposed to in the amniotic fluid. It may be a vestige of this.

It also is linked very closely with growth in lower animal species, because it is very close to growth hormone.

As you start to come up the evolutionary axis, it departs to an ever-greater degree and, in fact, it has an important metabolic role in lower

animal species that is not present at all in humans.

What we know about is the interaction between prolactin and reproduction, these other two being modulatory actions or prolactin. But this is the one that clinicians run into routinely.

If you look at the menstrual cycle, for those of you that might not be looking at it every day, it is divided into two phases -- the follicular phase, where the major agenda here is ripening of the dominant follicle and mounting of an estrogen response with that follicle that, in turn, evokes the mid-cycle gonadotropin surge.

The second half -- and this is where prolactin is terribly important in the rodent -- is the maintenance of the corpus luteum and progesterone secretion.

It has little or no effect in the human in this regard. It is the major luteotropic hormone of a rodent. It has little to do with the corpus luteum function of the human in physiologic ranges.

If you then look at it across the cycle, you begin to see the first problem you had with prolactin, and that is getting ambient prolactin levels in the follicular phase which I just mentioned, which is the minus days here up to the

mid-cycle surge, and in the luteal phase, which are the positive days.

The first thing that strikes you is that perhaps the luteal phase level might be a little bit high, but there is enormous scatter in this data. And that has to do with the non-specific effects of stress, time of day, which is shown in the next slide.

In fact, prolactin is a pulsatily secreted hormone, particular with high pulses of this at night. But these are sort of hourly samples. If you break these down into five and ten-minute samples, you will see that each one of these is comprised of a series of many pulses.

So, this episodic secretion confounds even the best attempts to get ambient prolactin level, as does stress.

In fact, if you look at this across sort of prolactin levels pre and post-natally, you see that once pregnancy ensues, prolactin levels immediately begin to rise. This is from two sources, one being the pituitary itself. As I mentioned, 30 percent or 40 percent of the pituitary becomes prolactin secreting cells in response to the rising estrogen levels over pregnancy.

And secondly, the placenta makes prolactin, in and of itself, for completely unknown reasons, but in fact maybe having something to do with the amniotic fluid environment, that not being well studied.

At the time of delivery, there is a dramatic fall as estrogen levels fall, assuming that there is no breast feeding. But in fact, if you have breast feeding and repeated suckling here, there is, in fact, a rise with every time that a mother nurses a child.

Also, note the levels here. These are quite realistic. During breast feeding, which is a known protective effect, I might add, for breast cancer, the prolactin levels get up into the hundreds repeatedly.

So, you see, in terms of physiologic causes of increased prolactin, pregnancy, the post-partum period, and suckling, particularly with nipple stimulation during suckling, give you prolactin levels routinely six and eight times a day that are at the level of, or greater than, the drug under consideration.

There are a few other physiologic stimuli that provide less elevations of the

prolactin level.

Now, going from the physiology of prolactin, in which the excursions, as I showed you, are quite into the pathologic ranges, let's move into what clinicians see, and you see all the time, as disruption of the reproductive cycle by increasing levels of prolactin which disrupt normal simplicity.

The first thing that you run into -- and this is very common in your specialty -- are a wide variety of drugs, of which the psychotropic agents are class specific. In fact, the class labeling has been devised for this.

But remember, there are several concerns out there in terms of oral contraceptives, alpha methyldopa, hampahypertensive medications, and a variety of other drugs which influence other biogenic amine receptors in the hypothalamus as well as other small polypeptide hormones and, of course, estrogen replacement therapy, in fact, as Dr. Temple mentioned.

In terms of that, these can be classed into groups, of which you are dealing with this particular set of receptors here. But you can see that cholinergic agents, catecholamines,

seratonergic agents, as a group, cause prolactin release that is elevated, substantial, and sustained.

And finally, as you look at ergot alkaloids and this particular agent which is, remember, a selective agent to the D2 subset of receptors, you have agents here which are less specific but cause either suppression or elevation of the serum prolactin.

The other thing is, what are the metabolic consequences of this and what are you like to see as clinicians with all of these drugs.

First of all, the menstrual cycle dysfunction may already be present in your patients at the time they present, or may ensue as they improve on these medications.

We see it all the time in infertility, largely because it creates inadequate luteal phases. And in the most severe cases, you see it in hypogonadism, with a loss of libido. And that is particularly manifested in the males, which cause infertility and hypogonadism. However, there is no known function for this agent in the males.

DR. TAMMINGA: Could we have the lights, please. Dr. Lin.

DR. LIN: Do you have any speculation as to why prolactin is more likely to cause cancer in rodents and less likely to cause cancer in human beings.

DR. CROWLEY: Yes. Fortunately, when I was on this committee, I was always glad for this other committee, the CAC committee, for considerations of what causes individual toxicities. And carcinogenicity, I think, has more to do with changes in the rodent population.

There is data that is quite substantial in this regard, to indicate that the incidence of carcinogenicity in the control animals in all of these studies have been rising over years.

So, I don't have an explanation for this in the lower animal studies, but I know there are some unique susceptibilities to the rat.

For example, the mice in these same studies are not susceptible to anything near the level that the rats are. And I believe there is evidence on this other committee, who unanimously agreed to this sort of assessment of this for specific carcinogenicity. I believe the company has some information about the fact that, over time, as we house animals and genetically screen for them,

the incidence of neoplasia in the control subjects is rising all of the time.

Now, that doesn't answer your question, which is, what is the added effect of prolactin, which is clearly there, and not to be avoided. But I think what we are doing is selecting a subset all the time in the controlled carcinogenicity studies in the lower animal primates.

Having said that, it is a major hormone in the primate, many of whose functions in the human are attenuated or even absent.

DR. TAMMINGA: Any other questions for Dr. Crowley. Thank you.

Comments from the committee.

I think you have our best opinion. Do you want more discussion, or is this all.

With that, we will close the committee meeting for today, thank Mr. Bernstein, who has been busy all day making sure the meeting has gone all right, and hope everybody is going to come back tomorrow.

(Whereupon, at 4:24 p.m., the meeting was recessed, to reconvene the following day, Tuesday, July 20, 1993.)

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